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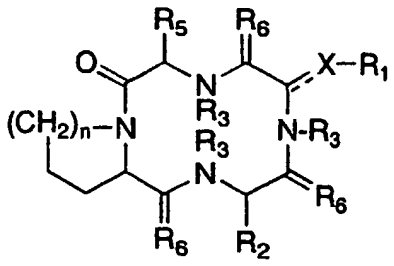
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(54) Title: APICIDIN-DERIVED CYCLIC TETRAPEPTIDES



(I)

(57) Abstract: Cyclic tetrapeptide compounds derived from apicidin therapeutically inhibit histone deacetylase activity and are represented by Formula (I).

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TITLE OF THE INVENTION

APICIDIN-DERIVED CYCLIC TETRAPEPTIDES

BACKGROUND OF THE INVENTION

Field of the invention

The present invention relates to anti-protozoal agents. In particular, the present invention relates to cyclic tetrapeptide compounds derived from apicidin that therapeutically inhibit histone deacetylase activity by protozoa.

Related background

Parasitic protozoa are responsible for a wide variety of infections in man and animals. Many of the diseases are life threatening to the host and cause considerable economic loss in animal husbandry. Malaria remains a significant health threat to humans despite massive international attempts to eradicate the disease. Trypanosomiasis such as i) Chagas disease caused by *Trypanosoma cruzi* and ii) African sleeping sickness caused by *T. brucei* are not uncommon in Africa and South America. Furthermore; opportunistic infections, caused by *Pneumocystis carinii*, *Toxoplasma gondii*, and *Cryptosporidium* sp., in immunocompromised hosts are becoming increasingly significant in developed countries.

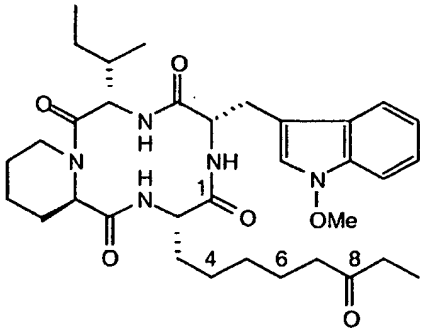
A protozoal infection of great economic importance is coccidiosis, a widespread disease of domesticated animals produced by infections by protozoa of the genus *Eimeria*. Some of the most significant of *Eimeria* species are those in poultry, namely *E. tenella*, *E. acervulina*, *E. necatrix*, *E. praecox*, *E. mitis*, *E. brunetti* and *E. maxima*. Coccidiosis can cause high levels of morbidity and mortality in poultry, resulting in extreme economic losses.

In some protozoal diseases, such as Chagas disease, there is no satisfactory treatment. In other protozoal diseases, drug-resistant strains of the protozoa may develop or have developed. Accordingly, there exists a continued need to identify new and effective anti-protozoal drugs. However, antiparasitic drug discovery has been, for the most part, a random and laborious process - through biological screening of natural products and synthetic compounds against a panel of parasites. Drug discovery can be greatly facilitated and made more directed if a specific target of antiprotozoal drugs can be identified, and incorporated into the screening process.

Histone deacetylase ("HDA") and histone acetyltransferase ("HAT") together control the net level of acetylation of histones. Inhibition of the action of HDA results in the accumulation of hyperacetylated histones, which in turn is implicated in a variety of cellular responses, including altered gene expression, cell differentiation and cell-cycle arrest. Recently, trichostatin A and trapoxin A have been reported as reversible and irreversible inhibitors, respectively, of mammalian HDA (see e.g., Yoshida et al., BioAssays, 17(5), 423-430 (1995)). Trichostatin A has also been reported to inhibit partially purified yeast HDA (Sanchez del Pino et al., Biochem. J., 303, 723-729 (1994)). Trichostatin A is an antifungal antibiotic and has been shown i) to have anti-trichomonal activity as well as cell differentiating activity in murine erythroleukemia cells, and ii) the ability to induce phenotypic reversion in *sis*-transformed fibroblast cells (see e.g., U.S. Patent No. 4,218,478; Yoshida et al., BioAssays, 17(5), 423-430 (1995); and references cited therein). Trapoxin A, a cyclic tetrapeptide, induces morphological reversion of v-*sis*-transformed NIH3T3 cells (Yoshida and Sugita, Jap. J. Cancer Res., 83(4), 324-328 (1992).

HDA inhibition as a target for cancer research is described in Saito et al., Proc. Natl Acad. Sci. USA, 96, 4592-4597(1999); Bernardi et al., Amino Acids 6, 315-318 (1994); and R.E. Shute et al., J. Med. Chem. 30, 71-78 (1987).

U.S. Patent No. 5,620,953 describes novel cyclic tetrapeptides, including apicidin. Apicidin [*cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl)] is a broad-spectrum antiprotozoal, antifungal and antineoplastic agent isolated from the fermentation culture of Fusarium fungus. The structure of apicidin is shown below:



Nevertheless, there remains a need to develop novel antiprotozoic compounds. The present inventors have found that a number of cyclic tetrapeptides

derived from apicidin, structurally related to trapoxin A, are inhibitors of histone deacetylase and possess antiprotozoal activity.

SUMMARY OF THE INVENTION

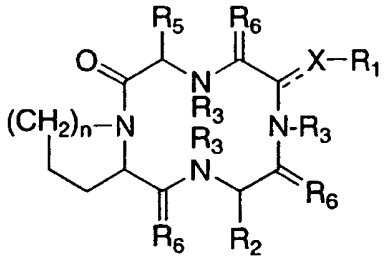
The present invention relates to novel cyclic tetrapeptides and pharmaceutical compositions containing the tetrapeptides. The invention also concerns a method for treating protozoal infections by administering to a host suffering from protozoal infection a therapeutically effective amount of a compound that inhibits histone deacetylase. Additionally, the invention relates to the use of known cyclic tetrapeptides to inhibit histone deacetylase activity and effective as antiprotozoal agents.

This invention relates i) to new antiprotozoal, antifungal and antineoplastic agents related to apicidin, ii) to processes for preparation of such novel agents, iii) to compositions containing such novel agents, iv) to the use of such novel agents in the treatment of parasitic infections, including malaria, in human and animals and v) the use of such novel agents in treating cancer.

In treating cancer the compounds of this invention can be used as cytostatic compounds, as agents in treating abnormal cell differentiation or proliferation, as agents against tumor growth, or as antimitotic agents for cancer chemotherapy.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, according to one embodiment, the present invention relates to a novel cyclic tetrapeptide represented by Formula I shown below:



I

or a pharmaceutically acceptable salt thereof wherein

	X is	(1)	$-CH_2-$,
		(2)	$-C(O)-$,
		(3)	$-CH(OR^a)-$,
		(4)	$=CH-$, or
		(5)	not present;
	n is	(1)	one, or
		(2)	two;
	R_1 is	(1)	R_7,
		(2)	$C(O)R_7$,
		(3)	CN,
		(4)	CO_2R^b,
		(5)	$C(O)N(OR^b)R^c$,
		(6)	$C(O)NR^cR^d$,
		(7)	$NHCO_2R^b$,
		(8)	$NHC(O)NR^cR^d$,
		(9)	$(C_0\text{-}C_4alkyl)OR^a$,
		(10)	$(C_0\text{-}C_4alkyl)OCO_2R^b$,
		(11)	$(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,
		(12)	$C(O)NR^cNR^cR^d$,
		(13)	$C(O)NR^cSO_2R^b$,
		(14)	$OS(O)_{ni}R_7$,
		(15)	$NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,
		(16)	a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, $(C_0\text{-}C_6alkyl)aryl$, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or

nitrogen, in which the nitrogen optionally has an R^c substituent,

(17) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(18) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent;

R_2 is

(1) optionally substituted C_2-C_{12}alkyl,

(2) optionally substituted C_2-C_{12}alkenyl,

(3) optionally substituted C_2-C_{12}alkynyl, or

(4) $(CH_2)_{nii}$-O-$(CH_2)_{mii}$ wherein nii, mii = 0 to 7,

wherein the optional substituents on the alkyl, alkenyl, and alkynyl are 1 to 8 groups and each group independently is

(a) CO_2R^a,
(b) $C(O)R^b$,
(c) $C(O)N(OR^b)R^c$,
(d) $C(O)NR^cR^d$,
(e) $C(O)NR^cNR^cR^d$,
(f) $C(O)NR^cSO_2R_7$,
(g) C_3-C_8cycloalkyl,
(h) C_2-C_5alkenyl,
(i) cyano,
(j) $=NOR^a$,
(k) $=NNR^bR^c$,
(l) $=NNR^bS(O)_{ni}R_7$,
(m) $N(OR^b)C(O)NR^bR^c$,
(n) $N(OR^b)C(O)R_7$,
(o) $NHC(O)N(OR^b)R^c$,
(p) $NR^cCO_2R^b$,
(q) $NR^cC(O)NR^cR^d$,
(r) $NR^cC(S)NR^cR^d$,
(s) $NR^cC(O)R_7$,
(t) $NR^bS(O)_{ni}R_7$,
(u) $NR^cCH_2CO_2R^a$,
(v) $NR^cC(S)R_7$,
(x) $NR^cC(O)CH_2OH$,
(y) $NR^cC(O)CH_2SH$,
(z) $NR^cCH_2CO_2R^a$,
(aa) $NR^cCH_2CH(OH)R_7$,
(bb) $NR^cP(O)(OR^a)R_7$,
(cc) NY^1Y^2, wherein Y^1 and Y^2 are independently H or C_1-C_{10}alkyl,
(dd) NO_2,
(ee) $N(OR^b)C(O)R^b$,
(ff) C_1-C_{10}alkanoylamino,
(gg) OR^a,
(hh) $OS(O)_{ni}R_7$,

(ii) oxo,
(jj) OCO_2R^b,
(kk) $OC(O)NR^cR^d$,
(ll) $P(O)(OR^a)_2$,
(mm) $P(O)(OR^a)R_7$,
(nn) $SC(O)R_7$,
(oo) $S(O)_{ni}R_7$,
(pp) SR_7,
(qq) $S(O)_{ni}NR^cR^d$,
(rr) $NR^cCH_2CO_2R^a$,
(ss) diazo,
(tt) C_1-C_5 perfluoroalkyl,
(uu) $B(O)(OR^a)OR^a$,
(vv) halogen,
(ww) aryl(C_0-C_5alkyl), wherein the aryl is optionally substituted with 1 to 3 groups, wherein each group independently is R^f, or
(xx) a 3- to 8-membered heterocycle containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is R^f, and the heterocycle may be saturated or partly unsaturated;

R_3 each independently is
(1) hydrogen,
(2) halogen,
(3) OR^a,
(4) C_1-C_4alkyl, or
(5) C_1-C_4aryl;

R_5 is
(1) isopropyl, or
(2) sec-butyl;

R_6 each independently is

(1) O,
(2) S, or
(3) H;

R7 is (1) hydrogen,
(2) optionally substituted C_2-C_{10}alkyl,
(3) optionally substituted C_2-C_{10}alkenyl,
(4) optionally substituted C_2-C_{10}alkynyl,
(5) optionally substituted C_3-C_8cycloalkyl,
(6) optionally substituted C_5-C_8cycloalkenyl,
(7) optionally substituted aryl,

wherein the optional substituents on the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl and aryl are 1 to 4 groups, and each group independently is

(a) C_1-C_5alkyl,
(b) X^1-C_1-C_{10}alkyl, wherein X^1 is O or $S(O)_{ni}$,
(c) C_3-C_8cycloalkyl,
(d) hydroxy,
(e) halogen,
(f) cyano,
(g) carboxy,
(h) NY^1Y^2, wherein Y^1 and Y^2 are independently H or C_1-C_{10}alkyl,
(i) nitro,
(j) C_1-C_{10}alkanoylamino,
(k) aroyl amino wherein the aroyl is optionally substituted with 1 to 3 groups wherein each group independently is R^{f1}, wherein R^{f1} is defined by any of the definitions below for R^f except for (14), (26), (27), and (32),
(l) oxo,
(m) aryl C_0-C_5alkyl wherein the aryl is optionally substituted with 1 to 3 groups, wherein each group independently is R^{f1},
(n) C_1-C_5perfluoroalkyl,

(o) $N(OR^b)C(O)R7'$, wherein R7' is any of the above definitions of R7 from (1) to (7)(n), and below of R7 from (8) to (12), or

(p) $NR^cC(O)R7'$,

(8) a 5- to 10-membered heterocycle containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen and the heterocycle is optionally substituted by 1 to 3 groups, each group independently is R^{f1}, and the heterocycle may be saturated or partly unsaturated,

(9) a benzene ring fused to a 5- to 10-membered heterocyclic ring containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen and the heterocycle is optionally substituted by 1 to 3 groups, each group independently is R^{f1}, and the heterocycle may be saturated or partly unsaturated,

(10) a 5- to 10-membered heterocyclic ring containing from 1 to 4 heteroatoms fused to a second 5- to 10-membered heterocyclic ring containing from 1 to 4 heteroatoms, each heteroatom in either heterocyclic ring independently is oxygen, sulfur or nitrogen and the second heterocyclic ring is optionally substituted by 1 to 3 groups, each group independently is R^{f1}, and each heterocycle independently may be saturated or partly unsaturated,

(11) a benzene ring fused to a C3-C8cycloalkyl ring, wherein the cycloalkyl is optionally substituted by 1 to 3 groups each independently being R^{f1}, and the cycloalkyl ring may be saturated or partly unsaturated, or

(12) a 5- to 10-membered heterocyclic ring containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen, the heterocyclic ring is fused to a C3-C8cycloalkyl ring, wherein the cycloalkyl ring is optionally substituted by 1 to 3 groups each independently being R^{f1}, and the cycloalkyl ring may be saturated or partly unsaturated,

R^a is (1) hydrogen,

(2) optionally substituted C_1-C_{10}alkyl,

(3) optionally substituted C_3-C_{10}alkenyl,
(4) optionally substituted C_3-C_{10}alkynyl,
(5) optionally substituted C_1-C_{10}alkanoyl,
(6) optionally substituted C_3-C_{10}alkenoyl,
(7) optionally substituted C_3-C_{10}alkynoyl,
(8) optionally substituted aroyl,
(9) optionally substituted aryl,
(10) optionally substituted C_3-C_7cycloalkanoyl,
(11) optionally substituted C_5-C_7cycloalkenoyl,
(12) optionally substituted C_1-C_{10}alkylsulfonyl,
(13) optionally substituted C_3-C_8cycloalkyl,
(14) optionally substituted C_5-C_8cycloalkenyl,

wherein the optional substituents on the C_1-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_1-C_{10}alkanoyl, C_3-C_{10}alkenoyl, C_3-C_{10}alkynoyl, aroyl, aryl, C_3-C_7cycloalkanoyl, C_5-C_7cycloalkenoyl, C_1-C_{10}alkylsulfonyl, C_3-C_8cycloalkyl and C_5-C_8cycloalkenyl are from 1 to 10 groups, wherein each group independently is hydroxy, C_1-C_6alkoxy, C_3-C_7cycloalkyl, aryl C_1-C_3alkoxy, NR^xR^x, CO_2R^b, $CONR^cR^d$, or halogen,

(15) C_1-C_5perfluoroalkyl,
(16) arylsulfonyl optionally substituted with 1 to 3 groups, wherein each group independently is C_1-C_5alkyl, C_1-C_5perfluoroalkyl, nitro, halogen or cyano,
(17) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, wherein each heteroatom is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 4 groups, wherein each group independently is C_1-C_5alkyl, C_1-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, and wherein the heterocycle may be saturated or partly unsaturated, or
(18) $OP(O)(OR^b)_2$;

R^b is
(1) H,
(2) optionally substituted aryl,
(3) optionally substituted C_1-C_{10}alkyl,

(4) optionally substituted C_3-C_{10}alkenyl,
(5) optionally substituted C_3-C_{10}alkynyl,
(6) optionally substituted C_3-C_{15}cycloalkyl,
(7) optionally substituted C_5-C_{10}cycloalkenyl, or
(8) optionally substituted 5- to 10-membered heterocycle containing 1 to 4 heteroatoms, wherein each heteroatom independently is oxygen, sulfur, or nitrogen,

wherein the optional substituents on the aryl, C_1-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl l, C_3-C_{15}cycloalkyl, C_5-C_{10}cycloalkenyl, or 5- to 10-membered heterocycle are from 1 to 10 groups, wherein each group independently is

(a) hydroxy,
(b) C_1-C_6alkyl,
(c) oxo,
(d) $SO_2NR^xR^x$,
(e) aryl C_1-C_6alkoxy,
(f) hydroxy C_1-C_6alkyl,
(g) C_1-C_{12}alkoxy,
(h) hydroxy C_1-C_6alkoxy,
(I) amino C_1-C_6alkoxy,
(j) cyano,
(k) mercapto,
(l) (C_1-C_6alkyl)-$S(O)_{ni}$-(C_0-C_6alkyl),
(m) C_3-C_7cycloalkyl optionally substituted with 1 to 4 groups, wherein each group independently is R^e,
(n) C_5-C_7cycloalkenyl,
(o) halogen,
(p) C_1-C_5alkanoyloxy,
(q) $C(O)NR^xR^x$,
(r) CO_2R^i,
(s) formyl,
(t) $-NR^xR^x$,
(u) 5 to 9-membered heterocycle, which may be saturated or partially unsaturated, containing from 1 to 4 heteroatoms,

wherein each heteroatom independently is oxygen, sulfur or nitrogen, and the heterocycle is optionally substituted with 1 to 5 groups, wherein each group independently is R^e,

(v) optionally substituted aryl, wherein the optional substituents are 1,2-methylenedioxy or 1 to 5 groups, wherein each group independently is R^e,

(x) optionally substituted aryl C_1-C_3alkoxy, wherein the optional substituents are 1,2-methylenedioxy or 1 to 5 groups, wherein each group independently is R^e, or

(y) C_1-C_5perfluoroalkyl;

R^c and R^d are independently selected from R^b; or R^c and R^d together with the N to which they are attached form a 3- to 10-membered ring containing 0 to 2 additional heteroatoms, each additional heteroatom independently being oxygen, nitrogen, or $(O)_{ni}$ substituted sulfur, wherein the ring is optionally substituted with 1 to 3 groups, wherein each group independently is R^g, hydroxy, thioxo, or oxo;

R^e is

(1) halogen,

(2) C_1-C_7alkyl,

(3) C_1-C_3perfluoroalkyl,

(4) $-S(O)_mR^i$,

(5) cyano,

(6) nitro,

(7) $R^iO(CH_2)_v$-,

(8) $R^iCO_2(CH_2)_v$-,

(9) $R^iOCO(CH_2)_v$,

(10) optionally substituted aryl wherein the optional substituents are from 1 to 3 groups, wherein each group independently is halogen, C_1-C_6alkyl, C_1-C_6alkoxy, or hydroxy,

(11) $SO_2NR^xR^x$,

(12) CO_2R^x, or

(13) NR^xR^x;

R^f is

(1) C_1-C_4alkyl,

(2) X^1-C_1-C_4alkyl, wherein X^1 is O or $S(O)_{mi}$,

(3) C_2-C_4alkenyl,

(4) C_2-C_4 alkynyl,

(5) C_1-C_3perfluoroalkyl,

(6) NY^3Y^4, wherein Y^3 and Y^4 are each independently hydrogen, C_1-C_5alkyl, or SO_2R^b,

(7) hydroxy,

(8) halogen,

(9) C_1-C_5alkanoyl amino,

(10) (C_0-C_4alkyl)CO_2R^a,

(11) (C_0-C_4alkyl)$C(O)NR^bR^c$,

(12) (C_0-C_4alkyl)NY^5Y^6 wherein Y^5 and Y^6 together with the N to which they are attached form a 3- to 7-membered ring containing 0 to 2 additional heteroatoms, wherein the additional heteroatoms independently are oxygen, nitrogen, or $(O)_{mi}$ substituted sulfur, wherein the ring is optionally substituted with 1 to 3 groups, wherein each group independently is R^e or oxo,

(13) (C_0-C_4alkyl)NO_2,

(14) (C_0-C_4alkyl)$C(O)R_7$,

(15) (C_0-C_4alkyl)CN,

(16) oxo,

(17) (C_0-C_4alkyl)$C(O)N(OR^b)R^c$,

(18) (C_0-C_4alkyl)$C(O)NR^cR^d$,

(19) (C_0-C_4alkyl)$NHC(O)OR^b$,

(20) (C_0-C_4alkyl)$NHC(O)NR^cR^d$,

(21) (C_0-C_4alkyl)OR^a,

(22) (C_0-C_4alkyl)OCO_2R^b,

(23) (C_0-C_4alkyl)$OC(O)NR^cR^d$,

(24) (C_0-C_4alkyl)$C(O)NR^cNR^cR^d$,

(25) (C_0-C_4alkyl)$C(O)NR^cSO_2R^b$,

(26) (C_0-C_4alkyl)$OS(O)_{ni}R_7$,

(27) (C_0-C_4alkyl)$NR^bS(O)_{ni}R_7$,

(28) C_0-C_4alkyl halogen,

(29) (C_0-C_4alkyl) SR^a,

(30) $P(O)(OR^a)_2$,

(31) C_0-C_4alkyl azide,

(32) C_0-C_4aryl substituted with from 1 to 4 groups, wherein each group independently is $S(O)_2R_7$, or

(33) C_0-C_4aryl where the aryl group is optionally substituted from 1 to 4 groups, wherein each group independently is CO_2R^b, $C(O)NR^cR^d$, NO_2, halogen, $OC(O)R^a$, OR^a or C_1-C_4alkyl;

R^g and R^h together with the N to which they are attached form a 3- to 7-membered ring containing 0 to 2 additional heteroatoms, wherein each additional heteroatom independently is oxygen, nitrogen, or $(O)_{mi}$ substituted sulfur, and the ring is optionally substituted with 1 to 3 groups, wherein each group independently is R^e or oxo; or

R^g and R^h are each independently

(1) hydrogen,

(2) C_1-C_6alkyl optionally substituted with hydroxy, amino, or CO_2R^i,

(3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C_1-C_7alkoxy, C_1-C_7alkyl, or C_1-C_3perfluoroalkyl,

(4) aryl C_1-C_6alkyl, wherein the aryl is optionally substituted with C1-C3perfluoroalkyl or 1,2-methylenedioxy,

(5) C_1-C_5alkoxycarbonyl,

(6) C_1-C_5alkanoyl,

(7) C_1-C_5alkanoyl C_1-C_6alkyl,

(8) arylC_1-C_5 alkoxycarbonyl,

(9) aminocarbonyl,

(10) (C_1-C_5monoalkyl)aminocarbonyl,

(11) (C_1-C_5dialkyl)aminocarbonyl, or

(12) CO_2R^b;

R^i is (1) hydrogen,

(2) C_1-C_3perfluoroalkyl,

(3) C_1-C_6alkyl, or

(4) optionally substituted aryl C_0-C_6alkyl, wherein the aryl optional substituents are from 1 to 3 groups, wherein each group independently is halogen, C_1-C_6alkyl, C_1-C_6alkoxy, or hydroxy;

R^x is a C_1-C_4alkyl;

m is 0 to 2;

mi is 0 to 2;

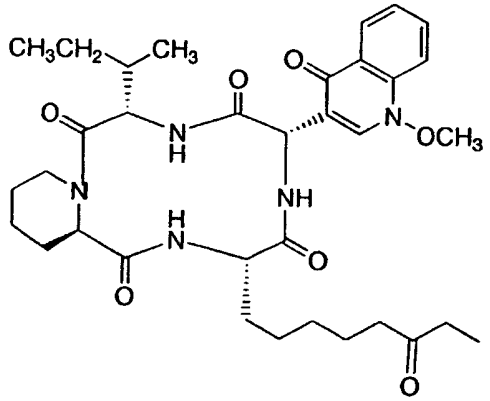
ni is 0 to 2;

mii is 0 to 7;

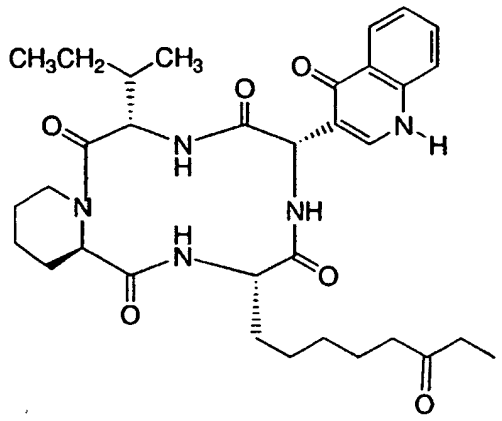
nii is 0 to 7;

v is 0 to 3; and

excluding apicidin, N-desmethoxy apicidin and compounds represented by the following chemical Formula IIA and Formula IIB:



IIA



IIB

Within this embodiment, the novel cyclic tetrapeptide of this invention includes a genus of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein:

X is	(1)	$-CH_2-$,	
	(2)	$-C(O)-$,	
	(3)	$-CH(OR^a)-$,	
	(4)	$=CH-$, or	
	(5)	not present; and	
R_1 is	(1)	R_7,	
	(2)	$C(O)R_7$,	
	(3)	CN,	
	(4)	CO_2R^b,	
	(5)	$C(O)N(OR^b)R^c$,	
	(6)	$C(O)NR^cR^d$,	
	(7)	$NHCO_2R^b$,	
	(8)	$NHC(O)NR^cR^d$,	
	(9)	$(C_0\text{-}C_4alkyl)OR^a$,	
	(10)	$(C_0\text{-}C_4alkyl)OCO_2R^b$,	

(11) $(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,

(12) $C(O)NR^cNR^cR^d$,

(13) $C(O)NR^cSO_2R^b$,

(13) $OS(O)_{ni}R_7$,

(14) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,

(15) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, $(C_0$-$C_6alkyl)aryl$, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(16) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(17) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is

oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

Within this genus there is a class of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein:

X is
(1) $-CH_2-$,
(2) $-C(O)-$,
(3) $-CH(OR^a)-$,
(4) $=CH-$, or
(5) not present;

R_1 is
(1) R_7,
(2) $C(O)R_7$,
(3) CN,
(4) CO_2R^b,
(5) $C(O)N(OR^b)R^c$,
(6) $C(O)NR^cR^d$,
(7) $NHCO_2R^b$,
(8) $NHC(O)NR^cR^d$,
(9) $(C_0\text{-}C_4alkyl)OR^a$,
(10) $(C_0\text{-}C_4alkyl)OCO_2R^b$,
(11) $(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,
(12) $C(O)NR^cNR^cR^d$,
(13) $C(O)NR^cSO_2R^b$,
(14) $OS(O)_{ni}R_7$,
(15) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,
(16) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, $(C_0\text{-}C_6alkyl)aryl$, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or

nitrogen, in which the nitrogen optionally has an R^c substituent,

(17) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(18) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent; and

R_2 is

(1) optionally substituted C_2-C_{12}alkyl,

(2) optionally substituted C_2-C_{12}alkenyl,

(3) optionally substituted C_2-C_{12}alkynyl, or

(4) $(CH_2)_{nii}$-O-$(CH_2)_{mii}$ wherein nii, mii = 0 to 7,

wherein the optional substituents on the C_2-C_{12}alkyl, C_2-C_{12}alkenyl, and C_2-C_{12}alkynyl are 1 to 8 groups and each group independently is

(a) CO_2R^a,

(b) $C(O)R^b$,

(c) $C(O)N(OR^b)R^c$,

(d) $C(O)NR^cR^d$,

(e) $C(O)NR^cNR^cR^d$,

(f) $C(O)NR^cSO_2R_7$,
(g) C_3-C_8cycloalkyl,
(h) C_2-C_5alkenyl,
(i) cyano,
(j) $=NOR^a$,
(k) $=NNR^bR^c$,
(l) $=NNR^bS(O)_{ni}R_7$,
(m) $N(OR^b)C(O)NR^bR^c$,
(n) $N(OR^b)C(O)R_7$,
(o) $NHC(O)N(OR^b)R^c$,
(p) $NR^cCO_2R^b$,
(q) $NR^cC(O)NR^cR^d$,
(r) $NR^cC(S)NR^cR^d$,
(s) $NR^cC(O)R_7$,
(t) $NR^bS(O)_{ni}R_7$,
(u) $NR^cCH_2CO_2R^a$,
(v) $NR^cC(S)R_7$,
(x) $NR^cC(O)CH_2OH$,
(y) $NR^cC(O)CH_2SH$,
(z) $NR^cCH_2CO_2R^a$,
(aa) $NR^cCH_2CH(OH)R_7$,
(bb) $NR^cP(O)(OR^a)R_7$,
(cc) NY^1Y^2, wherein Y^1 and Y^2 are independently H or C_1-C_{10}alkyl,
(dd) NO_2,
(ee) $N(OR^b)C(O)R^b$,
(ff) C_1-C_{10}alkanoylamino,
(gg) OR^a,
(hh) $OS(O)_{ni}R_7$,
(ii) oxo,
(jj) OCO_2R^b,
(kk) $OC(O)NR^cR^d$,
(ll) $P(O)(OR^a)_2$,
(mm) $P(O)(OR^a)R_7$,

(nn) $SC(O)R_7$,
(oo) $S(O)_{ni}R_7$,
(pp) SR_7,
(qq) $S(O)_{ni}NR^cR^d$,
(rr) $NR^cCH_2CO_2R^a$,
(ss) diazo,
(tt) C_1-C_5 perfluoroalkyl,
(uu) $B(O)(OR^a)OR^a$,
(vv) halogen,
(ww) aryl(C_0-C_5alkyl), wherein the aryl is optionally substituted with 1 to 3 groups, wherein each group independently is R^f, or
(xx) a 3- to 8-membered heterocycle containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is R^f, and the heterocycle may be saturated or partly unsaturated.

Within the above class of compounds, there is a subclass of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein n is 1 or 2.

Within this genus there is another class of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein:

X is (1) $-CH_2-$,
(2) $-C(O)-$, or
(3) not present; and

R_1 is (1) R_7,
(2) $C(O)R_7$,
(3) CN,
(4) CO_2R^b,
(5) $C(O)N(OR^b)R^c$,

(6) $C(O)NR^cR^d$,
(7) $NHCO_2R^b$,
(8) $NHC(O)NR^cR^d$,
(9) $(C_0\text{-}C_4alkyl)OR^a$,
(10) $(C_0\text{-}C_4alkyl)OCO_2R^b$,
(11) $(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,
(12) $C(O)NR^cNR^cR^d$,
(13) $C(O)NR^cSO_2R^b$,
(14) $OS(O)_{ni}R_7$,
(15) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,
(16) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, $(C_0\text{-}C_6alkyl)aryl$, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,
(17) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or
(18) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1

to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

Within the above class of compounds, there is a subclass of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein n is 1 or 2.

Within this genus there is yet another class of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein:

X is
(1) $-CH_2-$,
(2) $-C(O)-$, or
(3) not present; and

R_1 is
(1) R_7,
(2) $C(O)R_7$,
(3) CO_2R^b,
(4) $C(O)N(OR^b)R^c$,
(5) $C(O)NR^cR^d$,
(6) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, (C_0-C_6alkyl)aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,
(7) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by

1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(8) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

Within the above class of compounds, there is a subclass of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein n is 1 or 2.

Within this genus there is yet another class of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein:

X is (1) $-CH_2-$,
(2) $-C(O)-$, or
(3) not present;

R_1 is (1) R_7,
(2) $C(O)R_7$,
(3) CO_2R^b,
(4) $C(O)N(OR^b)R^c$,
(5) $C(O)NR^cR^d$,

(6) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, (C_0-C_6alkyl)aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(7) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(8) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent;and

R_2 is (1) optionally substituted C_2-C_{12}alkyl,

(2) optionally substituted C_2-C_{12}alkenyl,

(3) optionally substituted C_2-C_{12}alkynyl, or

(4) $(CH_2)_{nii}$-O-$(CH_2)_{mii}$ wherein nii, mii = 0 to 7,

wherein the optional substituents on the C_2-C_{12}alkyl, C_2-C_{12}alkenyl, and C_2-C_{12}alkynyl are 1 to 5 groups and each group independently is

(a) CO_2R^a,

(b) $C(O)R^b$,

(c) $C(O)N(OR^b)R^c$,

(d) $C(O)NR^cR^d$,

(e) $C(O)NR^cNR^cR^d$,

(f) $C(O)NR^cSO_2R_7$,

(g) C_3-C_8cycloalkyl,

(h) C_2-C_5alkenyl,

(i) cyano,

(j) $=NOR^a$,

(k) $=NNR^bR^c$,

(l) $=NNR^bS(O)_{ni}R_7$,

(m) $N(OR^b)C(O)NR^bR^c$,

(n) $N(OR^b)C(O)R_7$,

(o) $NHC(O)N(OR^b)R^c$,

(p) $NR^cCO_2R^b$,

(q) $NR^cC(O)NR^cR^d$,

(r) $NR^cC(S)NR^cR^d$,

(s) $NR^cC(O)R_7$,

(t) $NR^bS(O)_{ni}R_7$,

(u) $NR^cCH_2CO_2R^a$,

(v) $NR^cC(S)R_7$,

(x) $NR^cC(O)CH_2OH$,

(y) $NR^cC(O)CH_2SH$,

(z) $NR^cCH_2CO_2R^a$,

(aa) $NR^cCH_2CH(OH)R_7$,

(bb) $NR^cP(O)(OR^a)R_7$,

(cc) NY^1Y^2, wherein Y^1 and Y^2 are independently H or methyl,

(dd) NO_2,

(ee) $N(OR^b)C(O)R^b$,

(ff) C_1-C_3alkanoylamino,

(gg) OR^a,
(hh) $OS(O)_{ni}R_7$,
(ii) oxo,
(jj) OCO_2R^b,
(kk) $OC(O)NR^cR^d$,
(ll) $P(O)(OR^a)_2$,
(mm) $P(O)(OR^a)R_7$,
(nn) $SC(O)R_7$,
(oo) $S(O)_{ni}R_7$,
(pp) SR_7,
(qq) $S(O)_{ni}NR^cR^d$,
(rr) $NR^cCH_2CO_2R^a$,
(ss) diazo,
(tt) C_1-C_5 perfluoroalkyl,
(uu) $B(O)(OR^a)OR^a$,
(vv) halogen,
(ww) aryl(C_0-C_5alkyl), wherein the aryl is optionally substituted with 1 to 3 groups, wherein each group independently is R^f, or
(xx) a 3- to 6-membered heterocycle containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is R^f, and the heterocycle may be saturated or partly unsaturated.

Within the above class of compounds, there is a subclass of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein n is 1 or 2.

Within this embodiment there is a second genus of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein:
R_3 each independently is

(1) hydrogen,
(2) halogen,
(3) OR^a,
(4) C_1-C_4alkyl, or
(5) C_1-C_4aryl; and

R^a is
(1) hydrogen,
(2) optionally substituted C_1-C_6alkyl,
(3) optionally substituted C_3-C_6alkenyl,
(4) optionally substituted C_2-C_4alkanoyl,
(5) optionally substituted C_3-C_4alkenoyl,
(6) optionally substituted aroyl,
(7) optionally substituted aryl,
(8) optionally substituted C_5-C_6cycloalkanoyl,
(9) optionally substituted C_1-C_4alkylsulfonyl,
(10) optionally substituted C_5-C_6cycloalkyl,
(11) optionally substituted C_5-C_6cycloalkenyl,

wherein the optional substituents on the C_1-C_6alkyl, C_3-C_6alkenyl, C_2-C_4alkanoyl, C_3-C_4alkenoyl, aroyl, aryl, C_5-C_6cycloalkanoyl, C_1-C_4alkylsulfonyl, C_5-C_6cycloalkyl and C_5-C_6cycloalkenyl are from 1 to 10 groups, wherein each group independently is hydroxy, methoxy, aryl methoxy, NR^xR^x, CO_2R^b, $CONR^cR^d$, or halogen,

(12) CF_3,
(13) arylsulfonyl optionally substituted with 1 to 3 groups, wherein each group independently is methyl, CF_3, nitro, halogen or cyano, or
(14) a 5- or 6-membered heterocycle containing 1 to 3 heteroatoms, wherein each heteroatom is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is methyl, CF_3, NMe_2, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, and wherein the heterocycle may be saturated or partly unsaturated.

Within this second genus is a class of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein:

R_3 each independently is

(1) hydrogen,

(2) halogen,

(3) OR^a,

(4) C_1-C_4alkyl, or

(5) C_1-C_4aryl;

R^a is

(1) hydrogen,

(2) optionally substituted C_1-C_6alkyl,

(6) optionally substituted C_3-C_6alkenyl,

(7) optionally substituted C_2-C_4alkanoyl,

(5) optionally substituted C_3-C_4alkenoyl,

(6) optionally substituted aroyl,

(7) optionally substituted aryl,

(8) optionally substituted C_5-C_6cycloalkanoyl,

(9) optionally substituted C_1-C_4alkylsulfonyl,

(10) optionally substituted C_5-C_6cycloalkyl,

(11) optionally substituted C_5-C_6cycloalkenyl,

wherein the optional substituents on the C_1-C_6alkyl, C_3-C_6alkenyl, C_2-C_4alkanoyl, C_3-C_4alkenoyl, aroyl, aryl, C_5-C_6cycloalkanoyl, C_1-C_4alkylsulfonyl, C_5-C_6cycloalkyl and C_5-C_6cycloalkenyl are from 1 to 10 groups, wherein each group independently is hydroxy, methoxy, aryl methoxy, NR^xR^x, CO_2R^b, $CONR^cR^d$, or halogen,

(12) CF_3,

(13) arylsulfonyl optionally substituted with 1 to 3 groups, wherein each group independently is methyl, CF_3, nitro, halogen or cyano, or

(14) a 5- or 6-membered heterocycle containing 1 to 3 heteroatoms, wherein each heteroatom is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is methyl, CF_3, NMe_2, $C(O)NR^cR^d$, cyano, CO_2R^b or

halogen, and wherein the heterocycle may be saturated or partly unsaturated.

X is (1) $-CH_2-$,

(2) $-C(O)-$,

(3) $=CH-$, or

(4) not present; and

R_1 is (1) R_7,

(2) $C(O)R_7$,

(3) CN,

(4) CO_2R^b,

(5) $C(O)N(OR^b)R^c$,

(6) $C(O)NR^cR^d$,

(7) $NHCO_2R^b$,

(8) $NHC(O)NR^cR^d$,

(9) $(C_0\text{-}C_4alkyl)OR^a$,

(10) $(C_0\text{-}C_4alkyl)OCO_2R^b$,

(11) $(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,

(12) $C(O)NR^cNR^cR^d$,

(13) $C(O)NR^cSO_2R^b$,

(14) $OS(O)_{ni}R_7$,

(15) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,

(16) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, $(C_0\text{-}C_6alkyl)aryl$, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(17) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-

C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(18) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

Within the above class of compounds, there is a subclass of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein n is 1 or 2.

Within this second genus is a class of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein:

R3 each independently is

(1) hydrogen,
(2) halogen,
(3) OR^a,
(4) C_1-C_4alkyl, or
(5) C_1-C_4aryl;);

R^a is
(1) hydrogen,
(2) optionally substituted C_1-C_6alkyl,
(3) optionally substituted C_3-C_6alkenyl,

(4) optionally substituted C_2-C_4alkanoyl,

(5) optionally substituted C_3-C_4alkenoyl,

(6) optionally substituted aroyl,

(7) optionally substituted aryl,

(8) optionally substituted C_5-C_6cycloalkanoyl,

(9) optionally substituted C_1-C_4alkylsulfonyl,

(10) optionally substituted C_5-C_6cycloalkyl,

(11) optionally substituted C_5-C_6cycloalkenyl,

wherein the optional substituents on the C_1-C_6alkyl, C_3-C_6alkenyl, C_2-C_4alkanoyl, C_3-C_4alkenoyl, aroyl, aryl, C_5-C_6cycloalkanoyl, C_1-C_4alkylsulfonyl, C_5-C_6cycloalkyl and C_5-C_6cycloalkenyl are from 1 to 10 groups, wherein each group independently is hydroxy, methoxy, aryl methoxy, NR^xR^x, CO_2R^b, $CONR^cR^d$, or halogen,

(12) CF_3,

(13) arylsulfonyl optionally substituted with 1 to 3 groups, wherein each group independently is methyl, CF_3, nitro, halogen or cyano, or

(14) a 5- or 6-membered heterocycle containing 1 to 3 heteroatoms, wherein each heteroatom is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is methyl, CF_3, NMe_2, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, and wherein the heterocycle may be saturated or partly unsaturated;

X is

(1) $-CH_2-$,

(2) $-C(O)-$,

(3) $=CH-$, or

(4) not present; and

R_1 is

(1) R_7,

(2) $C(O)R_7$,

(9) CO_2R^b,

(10) $C(O)N(OR^b)R^c$,

(11) $C(O)NR^cR^d$,

(12) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, (C_0-C_6alkyl)aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(13) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(14) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

Within the above class of compounds, there is a subclass of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein n is 1 or 2.

Within this embodiment there is a third genus of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein:
R_6 each independently is

(1) O,
(2) S, or
(3) H;

X is
(1) $-CH_2-$,
(2) $-C(O)-$,
(3) $=CH-$, or
(4) not present; and

R_1 is
(1) R_7,
(2) $C(O)R_7$,
(3) CN,
(4) CO_2R^b,
(5) $C(O)N(OR^b)R^c$,
(6) $C(O)NR^cR^d$,
(7) $NHCO_2R^b$,
(8) $NHC(O)NR^cR^d$,
(9) $(C_0\text{-}C_4alkyl)OR^a$,
(10) $(C_0\text{-}C_4alkyl)OCO_2R^b$,
(11) $(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,
(12) $C(O)NR^cNR^cR^d$,
(13) $C(O)NR^cSO_2R^b$,
(14) $OS(O)_{ni}R_7$,
(15) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,
(16) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, $(C_0\text{-}C_6alkyl)$aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or

nitrogen, in which the nitrogen optionally has an R^c substituent,

(17) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(18) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

Within this third genus is a class of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein n is 1 or 2.

Within this third genus is a class of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein:

R_3 each independently is

(1) hydrogen,

(2) halogen,

(3) OR^a,

(4) C_1-C_4alkyl, or

(5) C_1-C_4aryl;

R_6 each independently is

(1) O,

(2) S, or

(3) H;

X is (1) $-CH_2-$,

(2) $-C(O)-$,

(3) $=CH-$, or

(4) not present; and

R_1 is (1) R_7,

(2) $C(O)R_7$,

(3) CN,

(4) CO_2R^b,

(5) $C(O)N(OR^b)R^c$,

(6) $C(O)NR^cR^d$,

(7) $NHCO_2R^b$,

(8) $NHC(O)NR^cR^d$,

(9) $(C_0$-C_4alkyl$)OR^a$,

(10) $(C_0$-C_4alkyl$)OCO_2R^b$,

(11) $(C_0$-C_4alkyl$)OC(O)NR^cR^d$,

(12) $C(O)NR^cNR^cR^d$,

(13) $C(O)NR^cSO_2R^b$,

(14) $OS(O)_{ni}R_7$,

(15) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,

(16) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, (C_0-C_6alkyl)aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(17) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(18) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

Within the above class of compounds, there is a subclass of compounds represented by Formula I or a pharmaceutically acceptable salt thereof wherein n is 1 or 2.

In one aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein X is preferably $-CH_2-$.

In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein X is preferably $-C(O)-$.

In still another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein X is preferably not present.

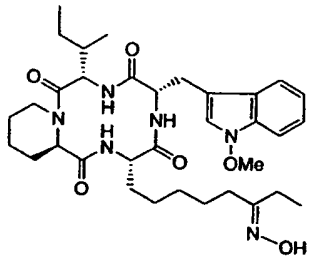
In yet another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein R_1 is preferably a 3- to 8-membered

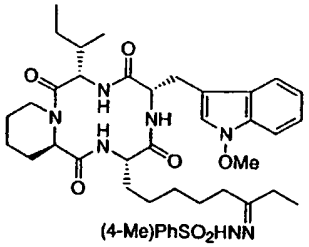
heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, (C_0-C_6alkyl)aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent.

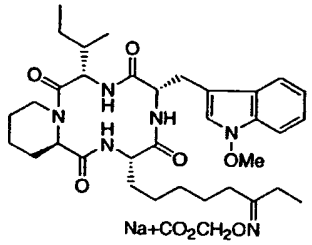
In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein R_1 is preferably a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide

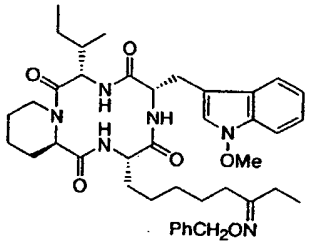
In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein R_1 is preferably a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

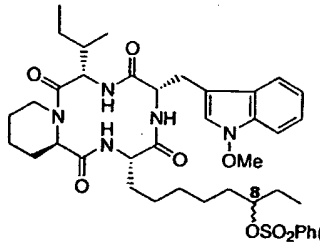
In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is Example 2, 3a, 3b, 3d, 10, 11, 12d, 12e, 17, or 18:

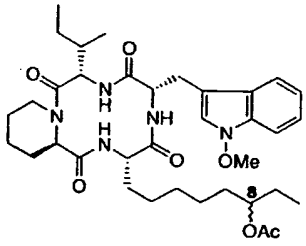


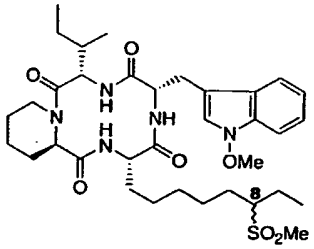

(4-Me)PhSO2HNN

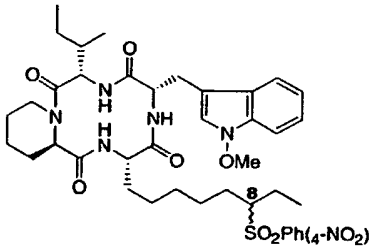

Na+CO2CH2ON

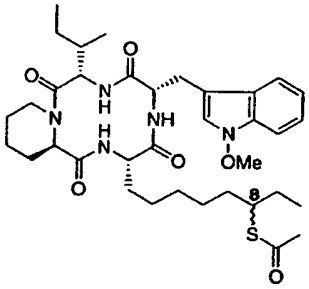

PhCH2ON


OSO2Ph(4-Me)

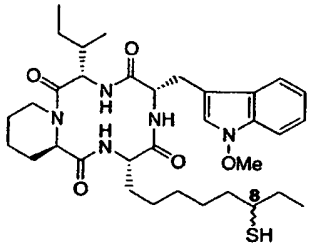

OAc


SO2Me

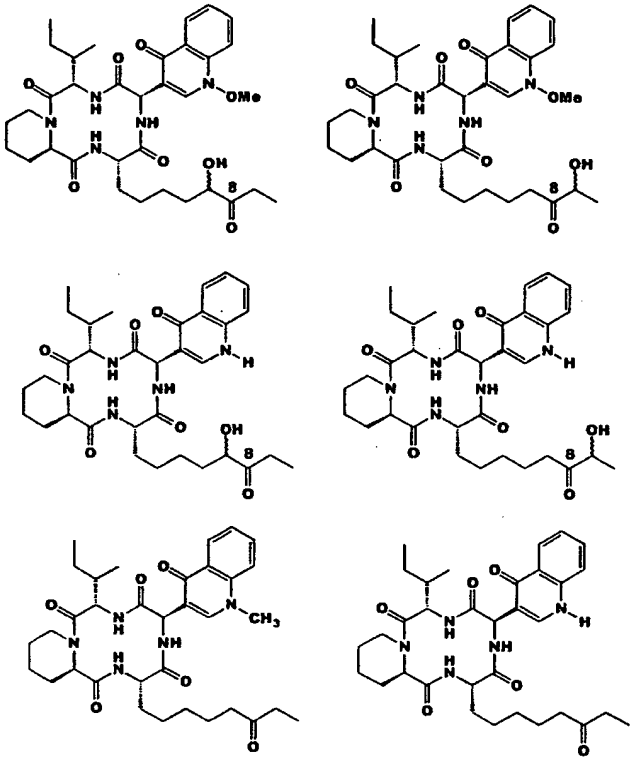

SO2Ph(4-NO2)

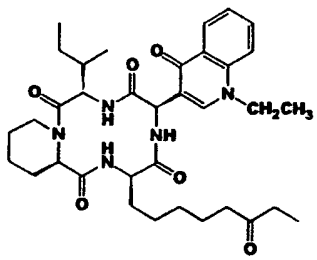
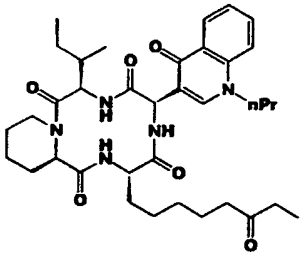
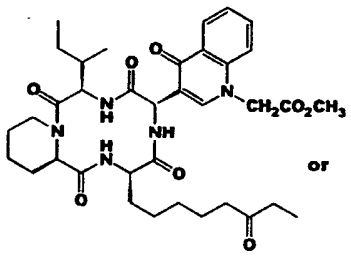


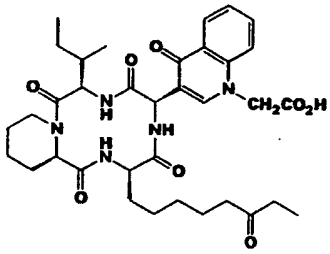
or


SH

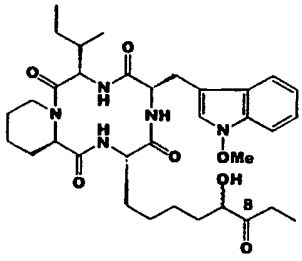
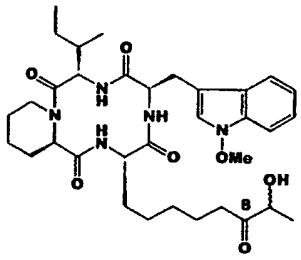
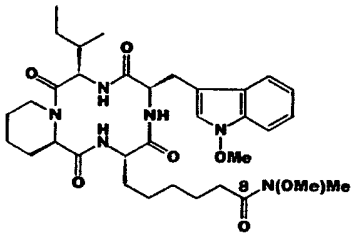
In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is Example 22a, 22b, 23a, 23b, 145, 146c, 146d, 146e, 146f, or 147:



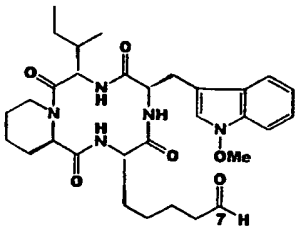
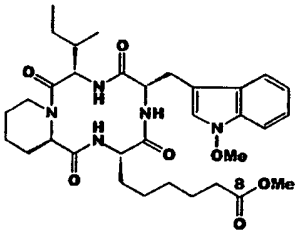
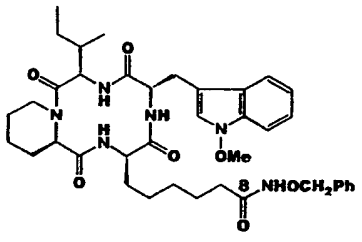




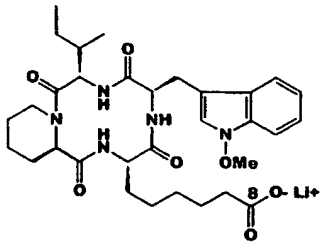
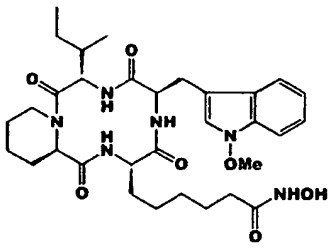
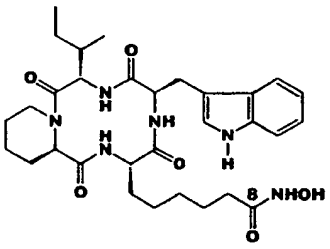
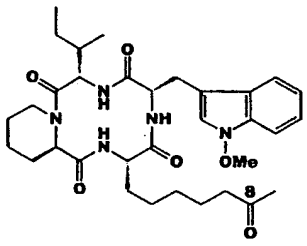
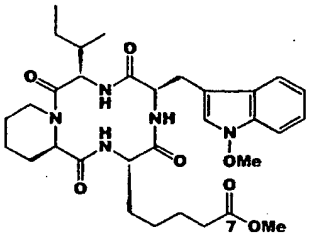
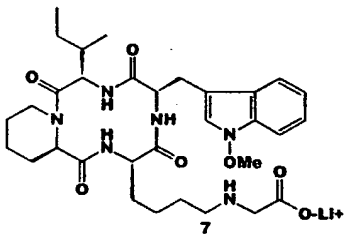
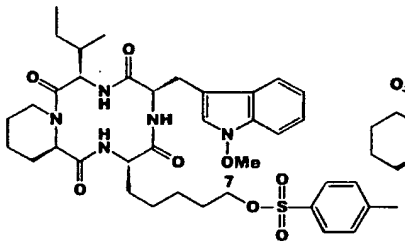
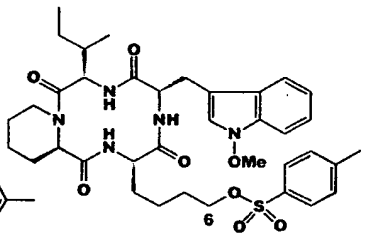
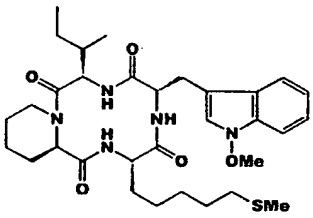


In yet another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is Example 21a, 21b, 24a, 24b, 26, 27, 28, 29, 30, 32, 37, 39, 43, 44, 46, 51, 56a, 63, 64, or 67:

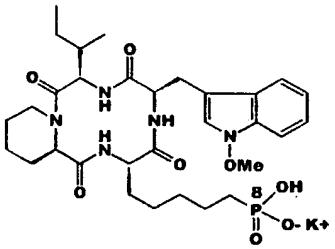
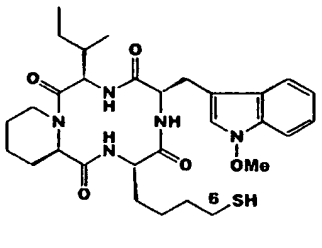
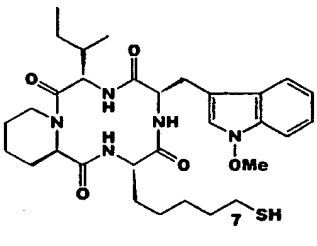




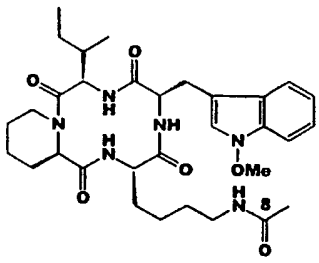
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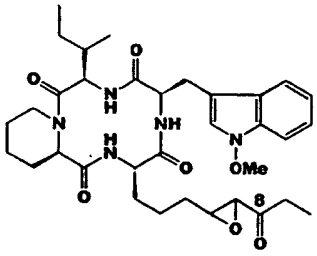










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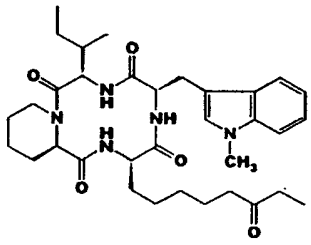




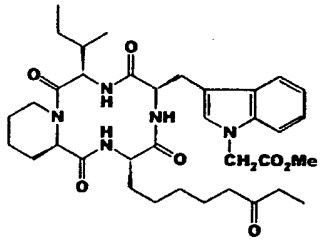


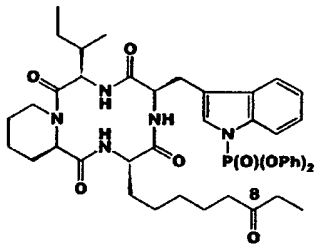
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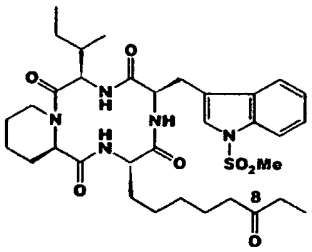


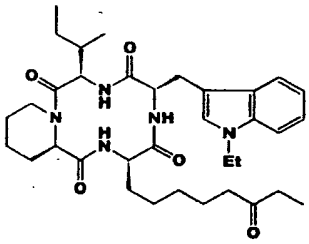
In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is Example 69, 70, 72, 73, 74a. 74b, 74c, 74d, 74e, 74f, 74g, 74h, 74i, 74j, 75, 79, 91, 93, 97, 98, 129a, or 129b:

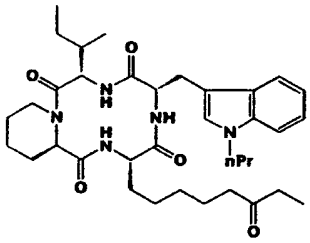


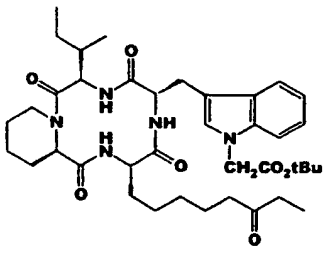


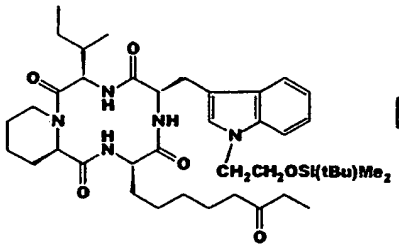


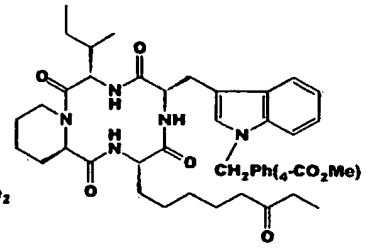


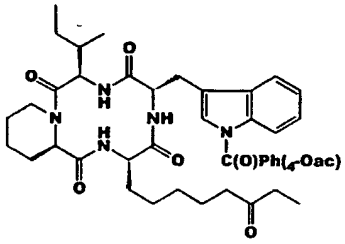


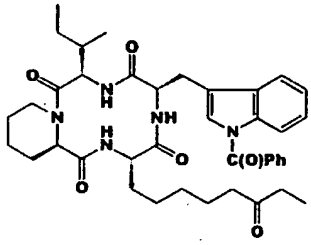


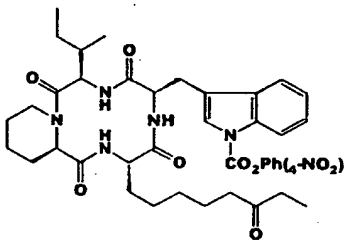

CH2CO2tBu

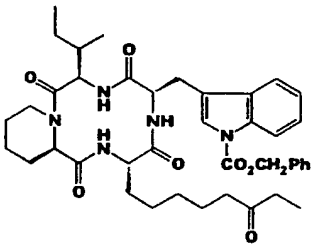

CH2CH2OSi(tBu)Me2

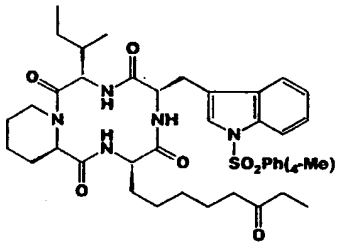

CH2Ph(4-CO2Me)

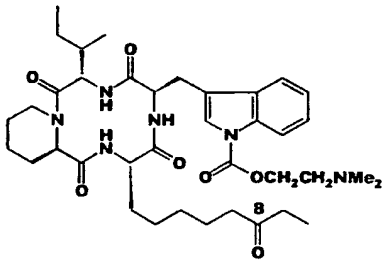

C(O)Ph(4-Oac)


C(O)Ph

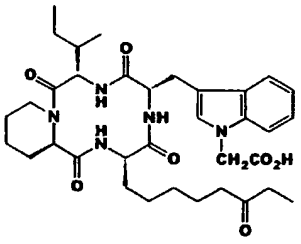

CO2Ph(4-NO2)

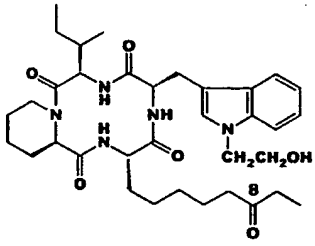

CO2CH2Ph

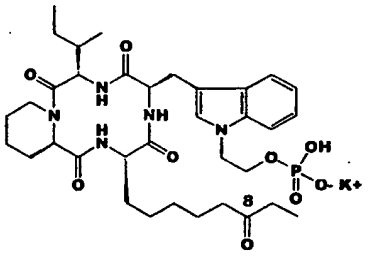

SO2Ph(4-Me)

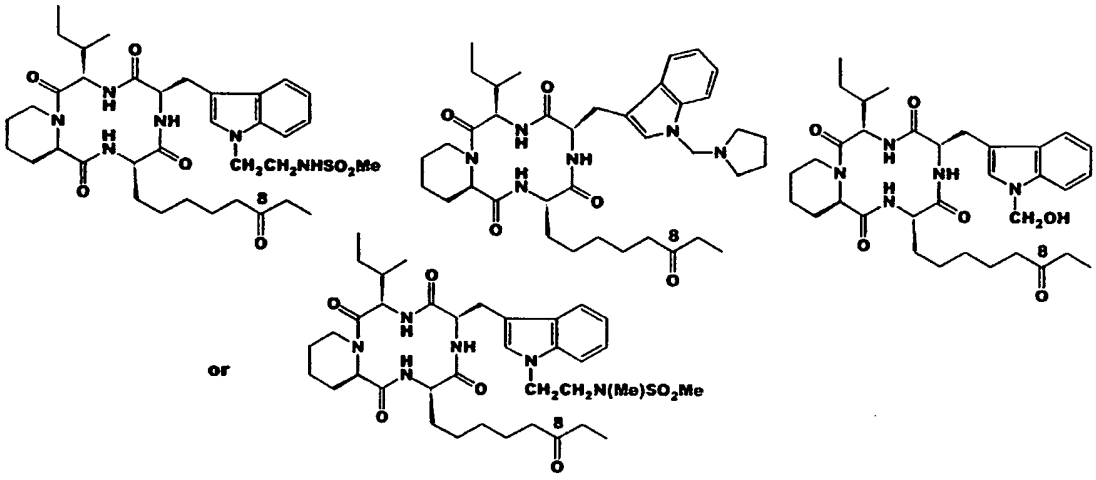

OCH2CH2NMe2

5


CH2CO2H


CH2CH2OH


OH
O- K+



In yet another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is Example 132a, 133, 135, 138, 139a, 139b, 139c, 139d, 139e, 139f, 139g, 139h, 139i, 139j, 140, 141, 142, 144b, 144d, 144f, 158, 159, 160, 162a, or 162b.

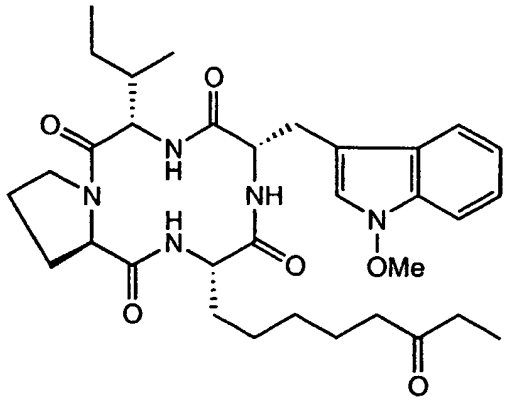
In still another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is Example 102, 103, 108a, or 108b.

In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is Example 109 or 110.

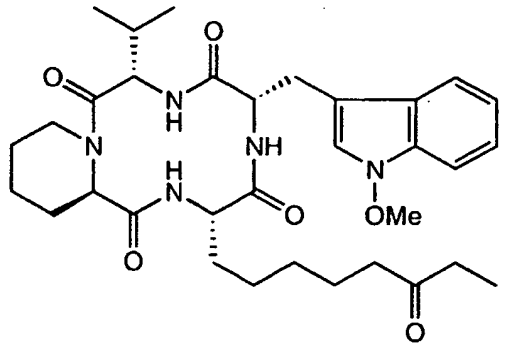
In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is Example 168.

In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is Example 156, 157a, 157b, 157c, or 157d.

In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is



In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is



In another aspect, the present invention provides a novel cyclic tetrapeptide represented by Formula I, wherein the compound is Example 153 or 154.

In another aspect, the present invention provides a method for the treatment of protozoal infections comprising the step of administering to a host suffering from a protozoal infection a therapeutically effective amount of the novel compounds of the invention which inhibits histone deacetylase. A therapeutically effective amount is that safe amount sufficient to inhibit histone deacetylase activity of the causative protozoa to control and overcome the infection. The present invention also provides a method for the prevention of protozoal infections comprising the step of administering to a host an effective preventative amount of the

novel compounds of the invention, which inhibits histone deacetylase. An effective preventative amount is that safe amount sufficient to inhibit the infection of the host.

In yet another aspect, the present invention provides a composition useful for the treatment or prevention of protozoal diseases which comprises an inert carrier and an effective amount of a compound of formula I.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "heterocycle", unless otherwise specified, means cyclic systems such as those described above for cycloalkyl and cycloalkenyl in which at least one atom is a sulfur, oxygen or nitrogen atom in a group of atoms that form the backbone of a ring. Such heterocycles include mono- or bicyclic compounds that are saturated or partly unsaturated, as well as benzo- or heteroaromatic ring fused saturated heterocycles or partly unsaturated heterocycles, and containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen. Examples of saturated heterocycles include morpholine, thiomorpholine, piperidine, piperazine, tetrahydropyran, tetrahydrofuran, dioxane, tetrahydrothiophene, oxazolidine, pyrrolidine; examples of partly unsaturated heterocycles include dihydropyran,

dihydropyridazine, dihydrofuran, dihydrooxazole, dihydropyrazole, dihydropyridine, dihydropyridazine and the like. Examples of benzo- or heteroaromatic ring fused heterocycle include 2,3-dihydrobenzofuranyl, benzopyranyl, tetrahydroquinoline, tetrahydroisoquinoline, benzomorpholinyl, 1,4-benzodioxanyl, 2,3-dihydrofuro(2,3-b)pyridyl and the like.

The term "aryl" is intended to include mono- and bicyclic aromatic and heteroaromatic rings containing from 0 to 5 heteroatoms independently selected from nitrogen, oxygen and sulfur. The term "aryl" is also meant to include benzofused cycloalkyl, benzofused cycloalkenyl, and benzofused heterocyclic groups. Examples of "aryl" groups include phenyl, pyrrolyl, isoxazolyl, pyrazinyl, pyridinyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidinyl, pyridazinyl, pyrazinyl, naphthyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furo(2,3-B)pyridyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, benzothiophenyl, quinolinyl, indolyl, 2,3-dihydrobenzofuranyl, benzopyranyl, 1,4-benzodioxanyl, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphthalene and the like.

Aroyl means arylcarbonyl in which aryl is as defined above.

Examples of NR^cR^d or NR^gR^h forming a 3- to 10- membered ring containing 0 to 2 additional heteroatoms selected from O, $S(O)_m$ and N are aziridine, azetidine, pyrrolidine, piperidine, thiomorpholine, morpholine, piperazine, octahydroindole, tetrahydroisoquinoline and the like.

The term "C_0" means that the carbon is not present. Thus, "C_0-C_5" means that there are from none to five carbons present – that is, five, four, three, two, one, or no carbons present.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring.

Compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the the course of the synthetic procedures used to prepare such compounds, or in using racemization or

epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

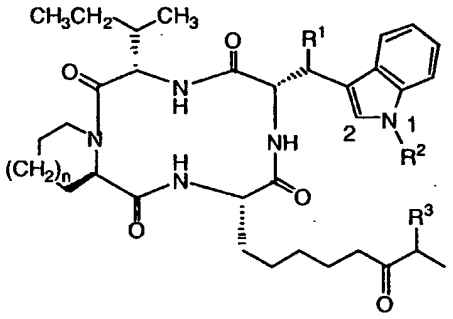
The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The concept of the inhibition of histone deacetylase as a target for antiprotozoal compounds is described in pending U.S. Patent Applications 09/296,834, filed April 22, 1999, and 08/716,978, filed September 20, 1996. Known compounds that may be histone deacetylase inhibitors and therefore useful in the treatment of protozoal diseases include, for example, trichostatin A, trapoxin A and B, HC-toxin, chlamydocin, Cly-2, WF-3161, Tan-1746, apicidin, and analogs thereof.

Trapoxin A is described in Itazaki et al., J. Antibiot. 43, 1524-1532(1990); HC-Toxin is described in Liesch et al., Tetrahedron 38, 45-48(1982); chlamydocin is described in Closse et al., Helv. Chim. Acta 57, 533-545(1974); Cly-2 is described in Hirota et al., Agri. Biol. Chem 37, 955-56(1973); WF-3161 is described in Umehana et al., J. Antibiot. 36, 478-483(1983); and Tan-1746 is described in Japanese Patent No. 7196686. Unlike the ethyl ketone sidechain found in apicidin, HC toxin, chlamydocin, trapoxin A and trapoxin B contain a C8 α-ketoepoxide functionality.

Apicidin and analogs thereof referred to herein are described by the following chemical formula:



Apicidin

Examples include

Compound	n	R^1	R^2	R^3
Apicidin Ia	1	H	OMe	H
Ib	0	H	OMe	H
Ic	1	H	OMe	OH
IIA	1	=O	OMe	H
IIB	1	=O	H	H

These compounds are described in pending U.S. Patent Application Nos. 08/281,325, filed July 27, 1994 and 08/447,664, filed May 23, 1995. The compounds are produced from a strain of *Fusarium* as disclosed in the applications.

The compounds of the present invention have been found to be histone deacetylase inhibitors. Accordingly, they can be useful in the treatment and prevention of protozoal diseases in human and animals, including poultry. Examples of protozoal diseases against which histone deacetylase inhibitors may be used, and their respective causative pathogens, include: 1) amoebiasis *(Dientamoeba* sp., *Entamoeba histolytica)*; 2) giardiasis *(Giardia lamblia)*; 3) malaria *(Plasmodium* species including *P. vivax, P. falciparum, P. malariae and P. ovale)*; 4) leishmaniasis *(Leishmania* species including *L. donovani, L. tropica, L. mexicana, and L. braziliensis)*; 5) trypanosomiasis and Chagas disease *(Trypanosoma* species including *T. brucei, T. theileri, T. rhodesiense, T. gambiense, T. evansi, T. equiperdum, T. equinum, T. congolense, T. vivax* and *T. cruzi)*; 6) toxoplasmosis *(Toxoplasma gondii)*; 7) neosporosis *(Neospora caninum)*; 8) babesiosis *(Babesia* sp.*)*; 9) cryptosporidiosis *(Cryptosporidium* sp.*)*; 10) dysentary *(Balantidium coli)*; 11) vaginitis *(Trichomonas* species including *T.vaginitis,* and *T. foetus)*; 12) coccidiosis *(Eimeria* species including *E. tenella, E. necatrix, E. acervulina, E. maxima and E. brunetti, E. mitis, E. bovis, E. melagramatis, and Isospora* sp.*)*; 13) enterohepatitis (*Histomonas gallinarum*); and 14) infections caused by *Anaplasma* sp., *Besnoitia* sp., *Leucocytozoan* sp., *Microsporidia* sp., *Sarcocystis* sp., *Theileria* sp., and *Pneumocystis carinii.*

The histone deacetylase inhibiting compounds and compositions of the present invention are preferably used in the treatment or prevention of protozoal infections caused by a member of the sub-phylum Apicomplexans. More preferably the compounds and compositions are used i) in the treatment or prevention of malaria, toxoplasmosis, cryptosporidiosis and trypanosomiasis in humans and animals, and ii) in the management of coccidiosis, particularly in poultry, either to treat coccidial infection or to prevent the occurrence of such infection.

When the histone deacetylase inhibiting compounds and compositions of this invention are administered on a chronic basis, such as in the prevention of coccidiosis in poultry, the histone deacetylase inhibitor preferably is selective for protozoal histone deacetylase over the host histone deacetylase. Such a selective inhibitor would minimize adverse histone deacetylase inhibition effects to the host over the long term.

Two specific examples of the method of this invention of administering an effective preventative amount of an histone deacetylase inhibitor to prevent the establishment of parasitic infections in humans and animals are 1) the

prevention of *Plasmodium* (malaria) infection in humans in endemic areas and 2) the prevention of coccidiosis in poultry. The histone deacetylase-inhibiting compound can be conveniently administered continually in the feed or drinking water, or regularly by oral or parenteral dosing.

Malaria is the number one cause of death in the world. The disease is transmitted by mosquitoes in endemic areas and can very rapidly progress to a life threatening infection. Therefore, individuals living in or visiting areas where malaria carrying mosquitoes are present routinely take prophylactic drugs to prevent infection. Thus, according to an embodiment of the present invention, a histone deacetylase inhibitor is administered orally or parenterally one or more time(s) a day, preferably each dose ranges from about 0.01mg/kg to about 100mg/kg. The compound may be administered for the entire period during which the patient or animal is at risk of acquiring a parasitic infection.

Coccidiosis is a disease that can occur in humans and animals and is caused by several genera of coccidia. The most economically important occurrence of coccidiosis is the disease in poultry. Coccidiosis in poultry is caused by protozoan parasites of the genus *Eimeria*. The disease can spread quite rapidly throughout flocks of birds via contaminated feces. The parasites destroy gut tissue and damage the gut lining, thereby impairing nutrient absorption. An outbreak of coccidiosis in a poultry house can cause such dramatic economic losses for poultry producers that it has become standard practice to use anticoccidial agents prophylactically in the poultry feed. Thus, according to another embodiment of this invention, a histone deacetylase inhibitor is administered in the feed or drinking water for the entire or a portion of the lifetime of domestic birds with a dose that ranges between about 0.1 ppm to about 500ppm in the feed or water.

For treatment of established parasitic infections in humans or animals, the histone deacetylase inhibitor is conveniently administered orally or parenterally when the infection is suspected or diagnosed. The treatment period varies according to the specific parasitic disease and the severity of the infection. In general the treatment is continued until the parasites are effectively eradicated and/or the symptoms of the disease are resolved. Two specific examples of the method of this invention for the treatment of protozoal infections by administering a therapeutically effective amount of a histone deacetylase inhibitor are 1) the treatment of a *Cryptosporidium parvum* infection in an animal or human and 2) the treatment of acute *Plasmodium falciparum* malaria in humans.

Cryptosporidium parvum is a protozoan parasite that infects and destroys cells lining the intestinal tract of humans and animals. The infection establishes quite rapidly and has acute effects on the patient. In the case of humans, patients get severe dysentery for a period of 5-7 days. In immune compromised patients *C. parvum* infections can persist and can be life threatening. In animals *C. parvum* infection is the leading cause of death in young dairy calves. A *C. parvum* infection can be easily diagnosed by symptoms and examination of a stool sample. When the disease is suspected and/or diagnosed, treatment with a histone deacetylase inhibitor according to the method of this invention can be initiated. The dose preferably ranges from about 0.01mg/kg to about 500mg/kg. The histone deacetylase is administered one or more time(s) a day, orally or parenterally until the infection is eliminated. The dosing period typically is in the range of about 1-3 weeks.

P. falciparum causes acute life threatening malarial infections in humans. The infection if left untreated can often result in the death of the patient. A malaria infection can be easily diagnosed by symptoms and examination of a blood sample from the patient. Treatment would be initiated following diagnosis. According to an embodiment of this invention, a histone deacetylase inhibitor is administered one or more time(s) a day, orally or parenterally, until the infection is eliminated. The dose preferably ranges from about 0.01mg/kg to about 200 mg/kg.

The histone deacetylase inhibiting compositions of this invention may be administered to a host in need of treatment in a manner similar to that used for other known antiprotozoal agents. For example, the compositions may be administered parenterally, orally, topically, or rectally. The dosage to be administered will vary according to the particular compound used, the infectious organism involved, the particular host, the severity of the disease, the physical condition of the host, and the selected route of administration; the appropriate dosage can be readily determined by a person skilled in the art. For the treatment of protozoal diseases in human and animals, the dosage preferably ranges from about 0.01mg/kg to about 500mg/kg. For prophylactic use in human and animals, the dosage preferably ranges from about 0.01mg/kg to about 100mg/kg. For use as an anticoccidial agent, particularly in poultry, the compound is preferably administered in the animals' feed or drinking water. The dosage preferably ranges from about 0.1ppm to about 500ppm.

In one aspect, the composition of the present invention comprises a histone deacetylase inhibitor and an inert carrier. The compositions include

pharmaceutical compositions for human and veterinary usage, and feed compositions for the control of coccidiosis in poultry.

The pharmaceutical compositions of the present invention comprise a histone deacetylase inhibitor as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the histone deacetylase inhibitor of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the histone deacetylase inhibitors may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations

such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 1 to about 500mg of the active ingredient.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing the histone deacetylase inhibiting compounds of this invention, via conventional processing

methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient.

As described above, to manage coccidiosis in poultry, the histone deacetylase inhibitor of this invention can be conveniently administered as a component of a feed composition. The poultry feed preferably contains from about 1ppm to about 1000ppm, more preferably from about 10ppm to about 150ppm of the histone deacetylase inhibitor of this invention. The optimum levels will vary with the species of *Eimeria* involved, and can be readily determined by one skilled in the art. It is preferred that the histone deacetylase inhibitor of this invention be added to poultry feed in the amount of from about 0.01% to about 0.1% by weight of the diet. The compositions of this invention are especially useful in controlling the pathology associated with *E. tenella*. The preferred concentration for similar control of intestinal-dwelling species is from about 0.01% to about 0.1% by weight of the diet. Amounts of about 0.01% to about 0.1% percent by weight are advantageous in reducing the pathogenic effects of both fecal coccidiosis and intestinal coccidiosis.

In the preparation of poultry feed incorporating the compositions of the invention, the histone deacetylase inhibitor can be conveniently dispersed, for example, by i) being mechanically mixed in a finely ground form with the poultry feedstuff, or ii) being first mixed with an intermediate formulation (to form a premix) that is subsequently blended with other poultry feedstuff components. Typical components of poultry feedstuffs include molasses, fermentation residues, corn meal, ground and rolled oats, wheat shorts and middlings, alfalfa, clover and meat scraps,

together with mineral supplements such as bone meal, calcium carbonate and vitamins.

Compositions containing a compound described by formula I may also be prepared in powder or liquid concentrate form. In accordance with standard veterinary formulation practice, conventional water-soluble excipients, such as lactose or sucrose, may be incorporated in the powders to improve their physical properties. It is preferable that the powder compositions of this invention comprise from about 50wt% to about 100wt%, and more preferably about 60wt% to about 80wt% of the compound. These powders may either be added to animal feedstuffs, for example, by way of an intermediate premix, or added to the animal drinking water by dilution.

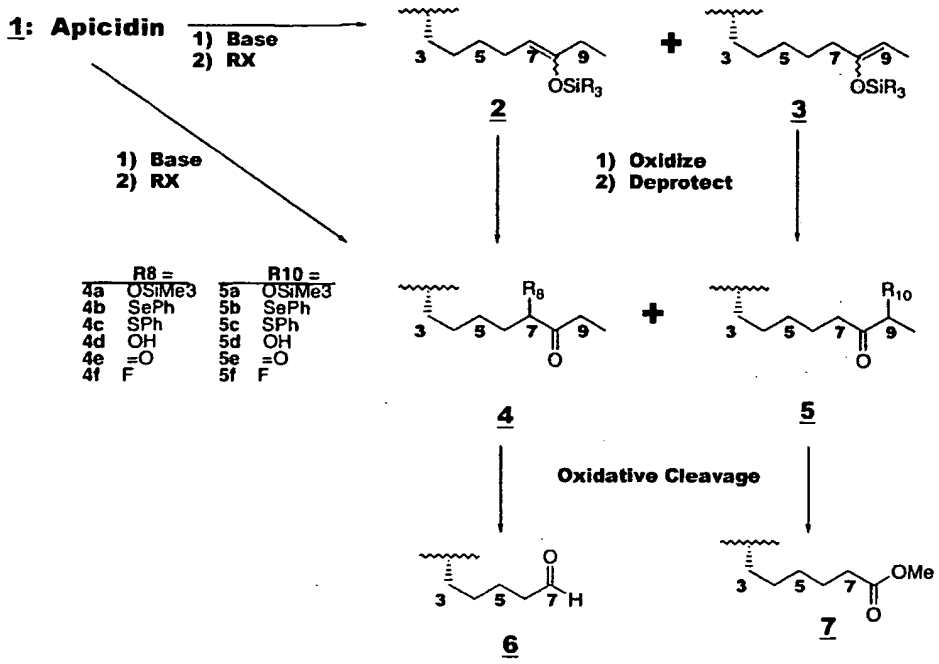
Liquid concentrates of this invention suitably contain a water-soluble compound combination and may optionally further include a veterinary acceptable water miscible solvent. For example, a solvent such as polyethylene glycol, propylene glycol, glycerol, or glycerol formal can be mixed with up to 30% v/v of ethanol. It is preferable that the liquid concentrates of this invention comprise from about 50wt% to about 100wt%, and more preferably about 60wt% to about 80wt% of the compound. The liquid concentrates may be administered to the drinking water of animals, particularly poultry.

The following examples are provided to more fully illustrate the present invention, and are not to be construed as limiting the scope of the claims in any manner.

Preparation of Side Chain-Modified Apicidin Analogs

Referring to Scheme I below, apicidin can be converted into alpha-substituted analog compounds **4** and **5**.

Scheme I



Apicidin is first enolized with an appropriate amine base including, but not limited to, LiN(*i*Pr)$_2$, NaN(SiMe3)$_2$, KN(SiMe3)$_2$, and the like at temperatures ranging from -78°C to 0°C to form an enolate. The amine base is preferably KN(SiMe3)$_2$. Appropriate solvents for this reaction include, but are not limited to, Et$_2$O, dioxane, tetrahydrofuran (THF), dimethoxyethane, and the like. The solvent is preferably THF. The enolate is reacted with an appropriate electrophile RX including, but not limited to, MeI, EtI, allyl bromide, benzyl bromide, PhSeCl, PhSCl, PhSSPh, (MeO)$_2$P(O)Cl, (CF$_2$SO$_2$)$_2$O, Et3SiCl, *t*Bu(Me)$_2$SiCl, (*n*Pr)3SiCl, Me3SiCl, Ph(Me)$_2$SiCl, and the like to form a silyl enol ether. The electrophile is preferably Me3SiCl.

Treatment of the thus prepared silyl enol ethers with an oxidant, including but not limited to, H$_2$O$_2$, *t*BuOOH, Me3SiOOH, AcOOH, dimethydioxirane and the like, or preferably MCPBA (meta-chloroperbenzoic acid), at temperatures from -78°C to RT (room temperature) but preferably 0°C to RT will produce the corresponding alpha-silyloxyketones, compounds **4a/5a**. The silyl

protecting groups can be then removed using a variety of acid or fluoride sources including, but not restricted to, HCl, H_2SO_4, HBF_4, acetic acid, PPTS (pyridinium *p*-toluenesulfonate), TsOH (*p*-toluenesulfonyl hydroxide), HF, HF•pyridine, or nBu_4NF and the like in protic or aprotic solvents including, but not limited to, CH_2Cl_2, $CHCl_3$, MeOH, EtOH, *i*PrOH, THF, Et_2O and dioxane and the like at temperatures from 0°C to 50°C to generate the alpha-hydroxyketones, compounds **4d/5d**.

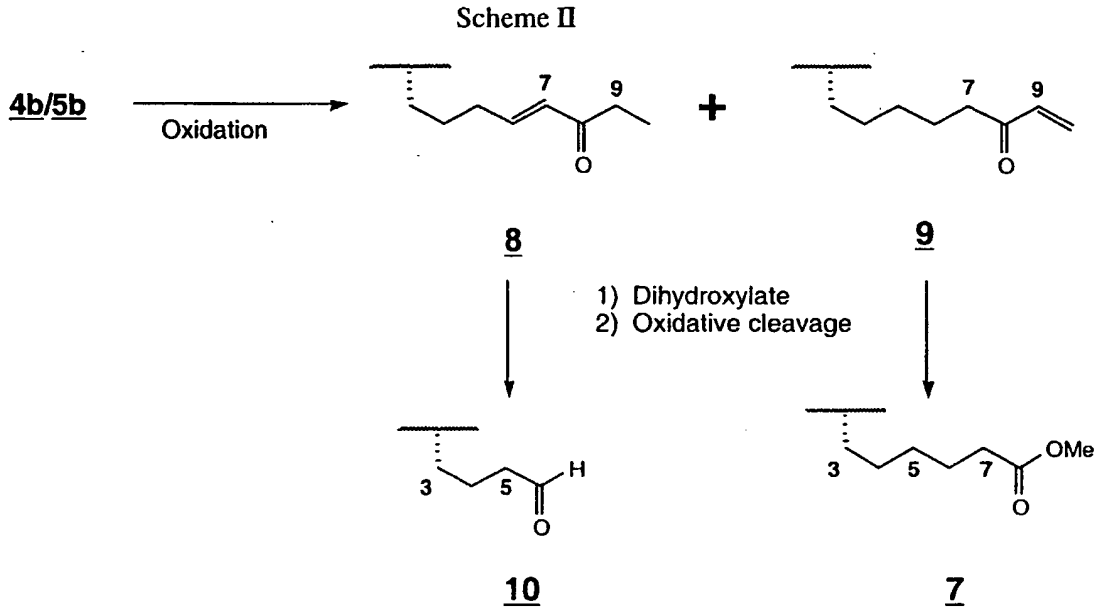
The alpha-hydroxyketone compounds **4d/5d** may be separated or used with no further separation, as desired. Compounds **4d/5d** can be oxidized to the corresponding diketones, compounds **4e/5e**, by treatment including, but not limited to, Swern oxidation, Dess-Martin oxidation, PCC (pyridinium chlorochromate), PDC (pyridinium dichromate), Moffat-oxidation, and the like, or most preferably TPAP/NMO (tetrapropylammonium perruthenate(VII)/4-methylmorpholine N-oxide) in solvents including, but not limited to, toluene, CH_2Cl_2, $CHCl_3$ and the like at temperatures ranging from -78°C to RT.

The alpha-hydroxyketone compounds **4d/5d** can be converted into the corresponding alpha-haloketone compounds such as **4f/5f** by treatment with Ph_3P/CBr_4, Ph_3P/I_2, PH_3P/CCl_4, $Ph_3P/CHCl_2CHCl_2$, DAST (diethylaminosulfur trifluoride), morpholinyl sulfur trifluoride, and the like in solvents such as CH_2Cl_2, $CHCl_3$, benzene, toluene and the like at temperatures from -78°C to RT.

The alpha-hydroxyketone compounds **4d/5d** can be treated with an oxidizing agent including, but not restricted to, $NaIO_4$, HIO_4, MnO_2, Amberlite® IRA-904 ion-exchange resin available from Aldrich Chemical Company, Milwaukee, Wisconsin, $NaIO_4$, KIO_4, and nBu_4NIO_4, or most preferably $Pb(OAc)_4$ to yield a C7-aldehyde compound **6**, and a C8-methyl ester compound **7**, by an oxidative cleavage reaction. The oxidative cleavage reaction may be performed in a variety of solvents or mixtures of solvents, including water, EtOH, *i*PrOH (isopropanol), *t*BuOH (tert-butanol), acetone, ether, THF, benzene, toluene, CH_2Cl_2, $CHCl_3$, and the like, or most preferably MeOH. Generally, the oxidative cleavage reaction is performed at temperatures from about -78°C to about 80°C. When utilizing MeOH, the reaction should be performed at temperatures from -20°C to RT. The oxidative cleavage reaction may be improved by the addition of a base, including but not restricted to $NaHCO_3$, Et_3N, $EtN(iPr)_2$, lutidine and the like, or most preferably pyridine. The oxidative cleavage reaction is generally complete in from about 5 minutes to about 24 hours.

Referring to Scheme II below, the phenylsulfide compounds **4c/5c** or phenylselenide compounds **4b/5b**, analogs of apicidin, are oxidized to the corresponding sulfoxide or selenoxide compounds (not shown) using reagents which include, but not limited to, Oxone, MCPBA, *t*BuOOH, AcOOH, $NaIO_4$, dimethyldioxirane, and the like, or most preferably H_2O_2, in solvents or mixtures of solvents, including, but not limited to toluene, $CHCl_3$, MeOH, water, or most preferably CH_2Cl_2 and at temperatures ranging from -20°C to 50°C.

Scheme II



Although the Scheme II shows only compounds **4b/5b** as the starting compounds, the same scheme applies just as well to using compounds **4c/5c** as starting compounds. The sulfoxides and selenoxides are thermally eliminated to generate the corresponding enone compounds **8** and **9** in solvents including, but not limited to, CH_2Cl_2, $CHCl_3$, MeOH, or most preferably toluene, at temperatures ranging from RT to 110°C.

Enone compounds **8** and **9** can be epoxidized (not shown) with appropriate epoxidizing agents including, but not limited to, dimethyldioxirane, H_2O_2, *t*BuOOH, AcOOH, and the like, or most preferably MCPBA, in solvents or

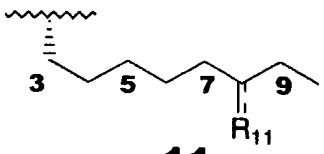
mixtures of solvents including, but not limited to, toluene, $CHCl_3$, MeOH, or most preferably CH_2Cl_2, at temperatures ranging from -20°C to RT.

Enone compounds **8** and **9** also may be dihydroxylated with OsO_4 under conditions known to those skilled in the art to form the corresponding diols. Osmium tetroxide may be used either stoichiometrically or catalytically in the presence of an oxidant including, but not restricted to, morpholine N-oxide, trimethylamine N-oxide, hydrogen peroxide, tert-butyl hydroperoxide and the like. The dihydroxylation reactions are performed in a variety of solvents or mixtures of solvents. The solvents include both protic and aprotic solvents such as water, MeOH, EtOH, tert-butanol, ether, THF, benzene, pyridine, acetone, and the like. The dihydroxylation reactions are performed at from -78°C to 80°C and are complete in from 5 minutes to 24 hours. The diol products thus obtained can be oxidatively cleaved as described previously for compounds **6** and **7** to yield a C6-aldehyde compound **10** and a C8 methyl ester compound **7** from compounds **8** and **9**, respectively.

Referring to Scheme III below, apicidin's sidechain C8-ketone group can be a starting point for analog synthesis.

Scheme III

1: Apicidin ⟶



11

R_{11} =	
11a:	OH
11b:	OH, R_{11b}
11c:	$OC(O)R_{11c}$ or $OC(S)R_{11c}$
11d:	OSO_2R_{11d}
11e:	H
11f:	$NR_{11f1}R_{11f2}$
11g:	$=NOR_{11g}$
11h:	$=NNHSO_2R_{11h}$
11i:	$=CR_{11i1}R_{11i2}$
11j:	epoxide
11k:	SR_{11k}

R_{11b}, R_{11c}, R_{11d}, R_{11f1}, R_{11f2}, R_{11g}, R_{11h}, R_{11i1}, R_{11i2}, and R_{11k} are each independently an alkyl or aryl group which optionally is substituted.

By Scheme III, the sidechain C8-ketone group can be reduced using reagents known to those skilled in the art, including, but not limited to $LiBH_4$, $LiAlH_4$, DIBAL-H (diisobutylaluminum hydride), K-Selectride® (potassium tri-*sec*-butylborohydride) available from Aldrich Chemical Company, Milwaukee, Wisconsin, L-Selectride® (lithium tri-*sec*-butylborohydride) available from Aldrich, Alpine-Borane® (B-isopinocampheyl-9-borabicyclo[3.3.1]-nonane) available from Aldrich, and the like or most preferably $NaBH_4$ to yield the C8 alcohol compound **11a**. These reduction reactions may be performed in protic or aprotic solvents including, but not limited to, THF, ether, dimethyl ether, dioxane, EtOH, CH_2Cl_2, EtOAc, $CHCl_3$, benzene, toluene, or most preferably MeOH, and at temperatures from -78°C to RT.

Apicidin's sidechain C8-ketone group can also be treated with RMgBr, RMgCl, RMgI, RLi, R_2CuLi, $RCeCl_2Li$ and the like to generate substituted alcohol compounds **11b**. In these RLi, RLiX, or RMgX type reactants, R is an alkyl or aryl group, and the alkyl and aryl groups are optionally substituted. These substitution reactions may be performed in solvents or mixtures of solvents, including but not limited to, Et_2O, dioxane, HMPA (hexamethylphosphoramide), DMSO, NMP (1-methyl-2-pyrrolidinone), dimethoxyethane, and the like, or most preferably THF, at temperatures from -78 °C to RT, and are complete in from 5 minutes to 12 hours.

The C8-alcohol compound **11a** generated above can be alkylated, acylated or sulfonylated using known methods for acylation, sulfonylation and alkylation of alcohols to generate apicidin derivative compounds **11c** or **11d**. Thus, acylation may be accomplished using reagents such as acid anhydrides, acid chlorides, chloroformates, carbamoyl chlorides, ClC(S)OPh(F_5), thiocarbonyldimidazole, isocyanates, and the like, and amine bases according to general procedures known to those skilled in the art. Sulfonylations may be carried out using sulfonyl chlorides or sulfonic anhydrides. Alkylations may be carried out using alkyl halides or trichloroacetimidates. Suitable solvents for these reactions include benzene, toluene, $CHCl_3$, CH_2ClCH_2Cl, and the like, or most preferably CH_2Cl_2, and may be performed from temperatures of -40°C to 80°C.

The hydroxyl group at C8 of compound **11a** can be eliminated using Burgess reagent, Martin's sulfurane reagent or by treating compound **11d** with a base

to generate a mixture of C6, C7- and C7, C8-olefin isomers. Suitable bases include, but are not limited to, Et_3N, $EtN(iPr)_2$, NaOMe, KO*t*Bu, and the like or most preferably DBU in solvents such as CH_2Cl_2, $CHCl_3$, toluene, benzene, MeOH, EtOH, pyridine and the like and at temperatures from 0°C to 110°C. The C8-hydroxyl group of compound **11a** can also be eliminated by reduction via the intermediary compound **11c** wherein R is OPh, $OPh(F_5)$, Set, and the like, or most preferably N-1-imidazolyl. Intermediary compound **11c** is treated with i) a radical initiator such as oxygen/Et_3B, AIBN (2,2'-azobisisobutyronitrile), benzoyl peroxide and the like, and ii) a hydride source, including, but not limited to, Et_3SiH, Me_3SnH, Ph_3SnH, Ph_3AsH, $n Bu_3SnCl/NaBH_4$, and the like, or most preferably $n Bu_3SnH$ in solvents including but not limited to CH_2Cl_2, $CHCl_3$, benzene, MeOH, EtOH, or most preferably toluene, and the like, at temperatures from -78°C to 110°C, to form compound **11e**.

Apicidin can be treated with mono- or disubstituted amines, a hydride source, and a proton source to generate compound **11f**. Suitable solvents include, but are not restricted to, benzene, toluene, EtOH, *i*PrOH and the like, or more preferably, MeOH. Suitable proton sources include, but are not limited to, TsOH, HCl, HCO_2H, PPTS and the like, or most preferably HOAc. The intermediate imine may be reduced *in situ* as it is formed or after azeotropic removal of water using a Dean-Stark trap. Suitable reducing agents include, but are not limited to, $LiAlH_4$, $NaBH_4$, $LiBH_4$, H_2/(10% Pd/C) and the like, or most preferably $NaBH_3CN$.

Oxime compound **11g** and hydrazone compound **11h** are prepared by treating apicidin with hydrazine in a solvent with a proton source. For example, apicidin can be treated with mono- or disubstituted amines, and a proton source. Suitable solvents include, but are not restricted to, benzene, toluene, EtOH, *i*PrOH and the like, or more preferably, MeOH. Suitable proton sources include, but are not limited to, TsOH, HCl, HCO_2H, PPTS and the like, or most preferably HOAc.

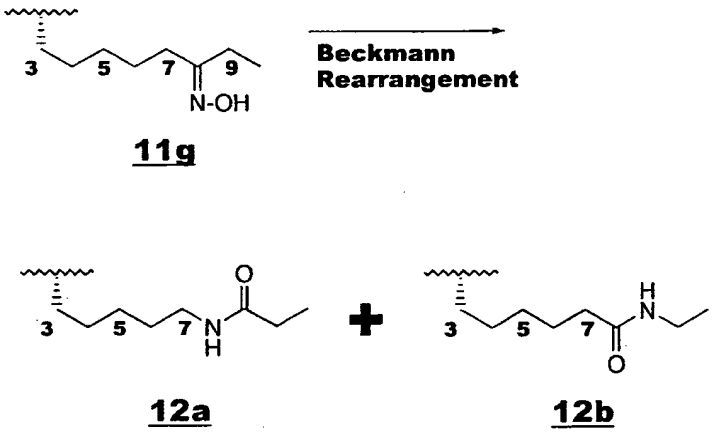
Apicidin is treated with stabilized Wittig reagents, unstabilized Wittig reagents or Horner-Emmons reagents to generate the unsaturated product, compound **11i**. Suitable reagents include, but are not limited to, $Ph_3P{=}CH_2$, $Ph_3P{=}CHMe$, $Ph_3P{=}CH(n Pr)$, $(MeO)_2P(O)CH_2CO_2Me$, $Ph_3P{=}CH_2C(O)Me$ and the like. These olefination reactions may be performed in solvents including, but not limited to, DMF (*N,N*-dimethylformamide), MeOH, CH_2Cl_2, toluene, Et_2O, MeCN, THF and the like and may be performed at from -78°C to 110°C. The C8 ketone of apicidin may be converted into an epoxide (compound **11j**) by treated with $CH_2{=}N_2$ or $Me_3SiCH{=}N_2$

in MeOH, or $Me_3S(O)I$ in a solvent such as *t*BuOH, dimethoxyethane, THF, DMF, DMSO, or more preferably HMPA and a strong base such a *t*BuOK, *n*BuLi, or more preferably NaH at temperatures from -78°C to 50°C.

Treatment of compound **11d** with an appropriate sulfur containing nucleophile permitted the introduction of sulfur at C8 to form compound **11k**. Suitable nucleophiles include NaSMe, KSAc, HSPh/Et_3N, $HSCH_2CH_2OH/EtN(iPr)_2$ and the like. These reactions proceed readily in polar solvents such as MeOH, EtOH, DMF, DMSO, HMPA, NMP and the like at temperatures from 0°C to 50°C.

Referring to Scheme IV below, a Beckmann rearrangement to form compounds **12a** and **12b** can be induced by treatment of compound **11g** with an acylating agent, including but not limited to, $POCl_3$, $SOCl_2$, $MeSO_2Cl$ and the like or more preferably TsCl and an amine base at temperatures from 0°C to 50°C. Suitable amine bases include Et_3N, $EtN(iPr)_2$, lutidine, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and the like, or most preferably pyridine. Pyridine also may serve as a solvent for this reaction or alternatively MeCN, benzene, toluene, dioxane and the like may be used.

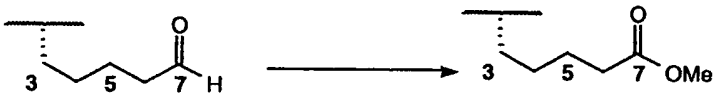
Scheme IV



Referring to Scheme V below, the C7-aldehyde compound **6** could be oxidized to the corresponding C7 methyl ester compound **13** by treating with suitable oxidants including NaOCl/HOAc/MeOH, *t*BuOCl/MeOH/pyridine, and the like, or

most preferably PDC/DMF/MeOH under conditions known in the art. The C7 methyl ester compound **13** can further serve as the starting material for additional derivatives. Similarly, the C6-aldehyde compound **10** can be oxidized to its corresponding C6 methyl ester (not shown).

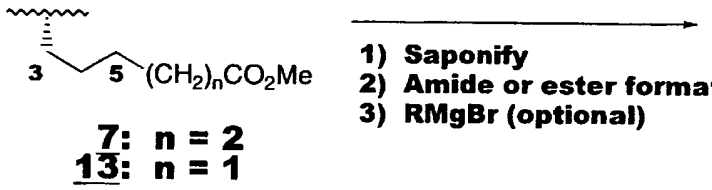
Scheme V



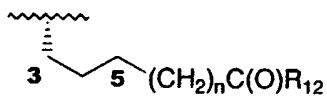
6 **13**

Referring to Scheme VI below, the methyl ester compounds **7** and **13** can be converted into a series of esters, amides and ketones.

Scheme VI



7: n = 2
13: n = 1



14 (n = 1 or 2)

R_{12} =

14a: OR_{14a}
14b: $NR_{14b1}R_{14b2}$
14c: H
14d: alkyl group
14e: aryl group

R_{14a}, R_{14b1}, and R_{14b2}, is each independently an alkyl or aryl group, which optionally is substituted.

Saponification could be accomplished by treating compound **7** with reagents including, but not limited to, NaOH, KOH, Me_3SiOOK, LiOOH and the like, or more preferably LiOH. Solvents, or mixtures of solvents, include MeOH, EtOH,

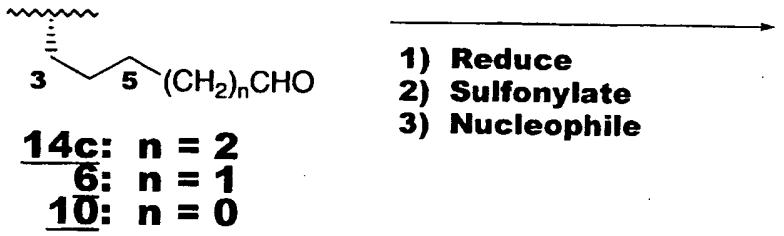
*t*BuOH, DMF, DMSO, HMPA, Et_2O, THF, water and the like. The reaction proceeds at temperatures from 0°C to 100°C. Amide and ester formation may be accomplished by reacting the C8-carboxylic acid (compound **14a**) thus prepared using standard ester- and amide-forming reagents known to those skilled in the art. The esterification reaction is carried out using at least one equivalent of an alcohol, HOR. Although preferably ten to one hundred equivalents of alcohol are used, the esterification also may be carried out using the alcohol as solvent. Esterification reagents include, but are not restricted to, dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl), diisopropylcarbodiimide, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorphosphate (BOP), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), chloro-tris-pyrrolidino-phosphonium hexafluorophosphate (PyClOP), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP), diphenylphosphoryl azide (DPPA), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), O-benzotriazol-1-yl-N,N,N',N'-bis(pentamethylene)uronium hexafluorophosphate and 2-chloro-1-methylpyridinium iodide. The ester-forming reactions may be facilitated by the optional addition of N-hydroxybenzotriazole, N-hydroxy-7-aza-benzotriazole, 4-(N,N-dimethylamino)pyridine or 4-pyrrolidinopyridine. The ester-forming reaction is generally performed using at least one equivalent (although several equivalents may be employed) of amine bases such as triethylamine, diisopropylethylamine, pyridine and the like. The carboxyl group may be activated for ester bond formation via its corresponding acid chloride or mixed anhydride, using conditions known to those skilled in the art. The ester-forming reaction is carried out in an aprotic solvent such as, for example, methylene chloride, tetrahydrofuran, diethyl ether, dimethylformamide, N-methylpyrrolidine, and the like, at temperatures ranging from -20°C to 60°C, and is complete in about 15 minutes to about 24 hours. Amides (where R_{12} is $NR_{14b1}R_{14b2}$) are prepared as described for esters (*vida supra*) from the corresponding carboxylic acids using and an appropriate amine, $HNR_{14b1}R_{14b2}$.

The amide compound **14b** (in which $NR_{14b1}R_{14b2}$ is N(OMe)Me) can be treated with nucleophilic agents to yield the corresponding aldehyde (compound **14c**) and ketones (compounds **14d** and **14e**). Suitable nucleophiles include, but are not limited to, hydride reagents, RLi or RMgX and the like as described above for the preparation of compounds **11a** and **11b**. In addition, the

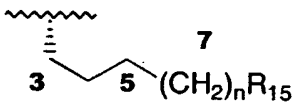
aldehyde and ketone products **14c, 14b and 14e** can be further reacted with hydride reagents, RLi or RMgX, to generate the corresponding alcohol adducts as described previously.

Referring to Scheme VII below, the aldehyde compounds **6**, **10** and **14c** serve as starting material for the preparation of a variety of derivatives.

Scheme VII



14c: n = 2
6: n = 1
10: n = 0



15 (n = 1, 2 or 3)

R_{15} =	
15a:	OR_{15a}
15b:	$S(O)_nR_{15b}$
15c:	N3
15d:	$NR_{15d1}R_{15d2}$
15e:	$P(O)(OR_{15e})_2$

R_{15a}, R_{15b}, R_{15d1}, R_{15d2}, and R_{15e}, are each independently an alkyl or aryl group which optionally is substituted.

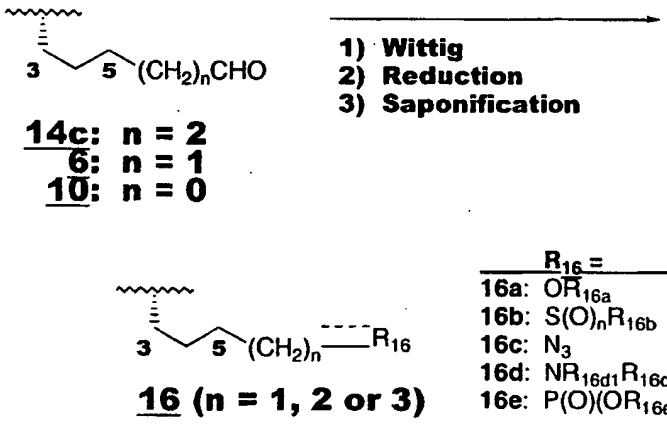
Reduction of the side chain aldehyde group in compounds **6**, **10** and **14c** with hydride reagents produced compound **15a** (where R_{15a} = H). The side chain alcohol thus obtained can then be sulfonylated, as described above in Scheme III. The sulfonyl group can then be displaced with an appropriate sulfur, nitrogen or phosphorous nucleophile to form compounds **15b**, **15c** and **15e** respectively. Suitable nucleophiles include NaSMe, KSAc, NaN_3, $(PhCH_2O)_2P(O)H$, $(P(OCH_2Ph)_3$, $(MeO)_2P(O)H$, $P(OMe)_3$ and the like.

Further, the side chain azide compound **15c** can be reduced using conditions known to those skilled in the art including, but not restricted to, H_2/10% Pd/C, HSAc/MeOH, $SnCl_2$, Ph_3P/H_2O and the like to form a side chain amine compound (not shown). The amine compound thus obtained can be acylated, alkylated or sulfonylated as described above. Alternatively, reductive amination of

the aldehyde compounds **6**, **10** and **14c** with a suitable amine as described above will generate the amine compound **15d**.

Referring to Scheme VIII below, the side chain of compounds **6**, **10** or **14c** can be extended by reacting the aldehyde with stabilized Wittig reagents, unstabilized Wittig reagents or Horner-Emmons reagents to form compound **16a**.

Scheme VIII



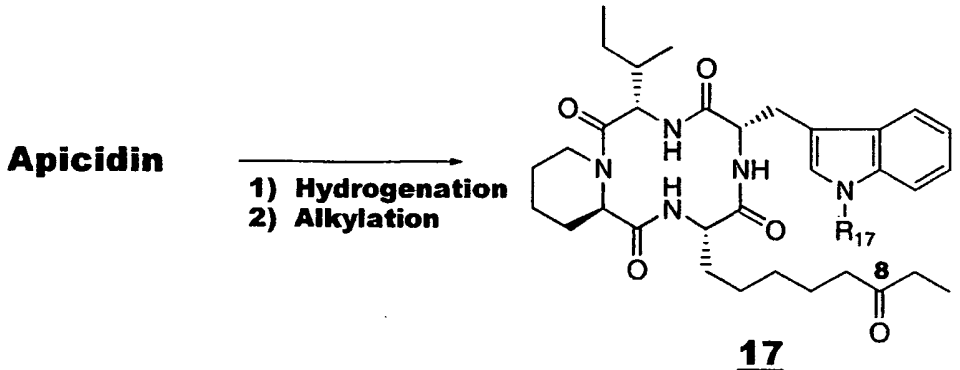
R_{16a}, R_{16b}, R_{16d1}, R_{16d2}, and R_{16e} are each independently an alkyl or aryl group, which optionally is substituted.

The side chain unsaturation of compound **16a** can be reduced by catalytic hydrogenation using conditions known to those skilled in the art. Suitable catalysts include 5% Pd/C, 10% Pd/C, $Pd(OH)_2$, PtO_2, $RhCl_3$, $RuCl_2(PPh_3)_3$, and the like. The hydrogenation reactions may be performed in solvents or mixtures of solvents including CH_2Cl_2, $CHCl_3$, toluene, MeOH, EtOH, EtOAc, acetone, THF, Et_2O, dimethoxyethane, DMF, DMSO, and the like. The reductions may be run at from one to 10 atmospheres of hydrogen pressure and the reactions are complete in from 5min to 24h. For apicidin analog compounds **16a** or **16b** in which R_{16a} or R_{16b} represents an ester moiety, the ester may be saponified and the carboxylic acid thus obtained may be converted into other esters or amides as described previously.

Referring to Scheme IX below, the N-methoxy group of apicidin may be removed by hydrogenation as described previously and the liberated indole nitrogen compound thus generated may be N-alkylated, acylated or sulfonylated using

known methods for acylation, sulfonylation and alkylation of indoles to generate apicidin derivative compound **17**.

Scheme IX



17

R_{17} is an alkyl or aryl group, which optionally is substituted.

Thus, acylation may be accomplished using reagents such as acid anhydrides, acid chlorides, chloroformates, carbamoyl chlorides, isocyanates and the like according to general procedures known to those skilled in the art. Sulfonylations may be carried out using sulfonyl chlorides or sulfonic anhydrides. Alkylations may be carried out using alkyl halides. Suitable bases for these acylation, sulfonylation and alkylation reactions include KH, *n*BuLi, *t*BuLi, LiN(*i*Pr)$_2$, NaN(SiMe3)$_2$, KN(SiMe3)$_2$ and the like or more preferably NaH. Suitable solvents, or mixtures of solvents for these reactions include benzene, toluene, $CHCl_3$, CH_2ClCH_2Cl, CH_2Cl_2, DMSO, HMPA, NMP and the like or most preferably DMF and may be performed from temperatures of -40°C to 80°C.

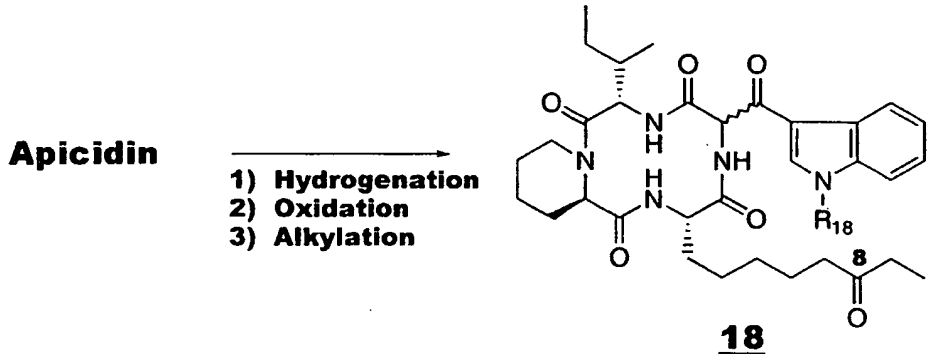
When the newly incorporated R_{17} group contains an ester moiety, the apicidin derivative compound **17** can be saponified to the corresponding carboxylic acid and converted into a series of amides using conditions described previously.

When the newly incorporated R_{17} group contains an alcohol function, the apicidin derivative compound **17**, can be acylated, alkylated, phosphorylated or sulfonylated as described previously. Alternatively, this alcohol function may be converted into a leaving group such as a sulfonate or halide and displaced with appropriate sulfur, nitrogen or phosphorus nucleophiles as described previously

Referring to Scheme X below, apicidin's tryptophan may be allylically

oxidized to generate beta-oxo apicidin analog compound **18** using conditions known to those skilled in the art. . **(What is R_{18}?)**

Scheme X



18

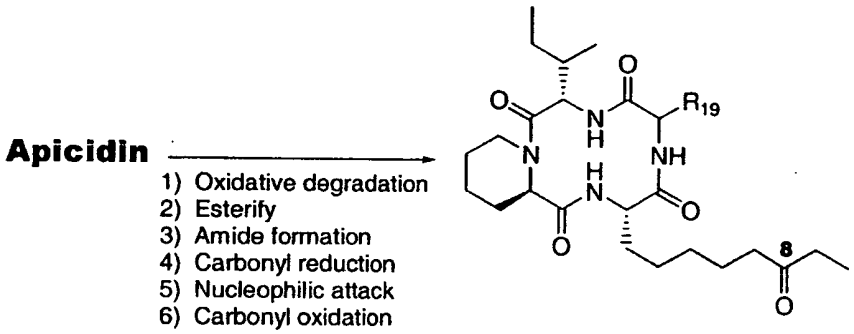
R_{18} is an alkyl or aryl group, which optionally is substituted.

Suitable oxidants include but are not restricted to *t*BuOOH, SeO_2, CrO_3, Na_2CrO_4, PCC, and the like, or more preferably DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone). Appropriate solvents, or mixtures of solvents, include DMF, toluene, benzene, CH_2Cl_2, $CHCl_3$, HOAc, pyridine, THF, MeOH, EtOH, water, and the like, or more preferably MeCN. These reactions are performed at from -20°C to 50°C and are complete in from 5min to 24h. The stereochemistry of the beta-oxo-tryptophan attachment of compound **18** may be changed by treatment with bases such as pyridine, $EtN(iPr)_2$, NaH, KH, DBU, lutidine, or most preferably Et_3N. The epimerization reaction proceeds at from 0°C to 50°C in solvents including $CHCl_3$, CH_2ClCH_2Cl, MeOH, EtOH, DMF, DMSO, NMP, and the like, or most preferably CH_2Cl_2. The nitrogen of the beta-oxo-tryptophan may be alkylated, acylated, sulfonylated or phosphorylated as described previously.

The beta-oxo carbonyl of compound **18** may be selectively reduced using a hydride source under radical conditions. Suitable hydride sources include Me_3SnH, *n*$Bu_3SnCl/NaBH_4$, Ph_3SnH, Ph_3AsH, and the like, or most preferably *n*Bu_3SnH, in the presence of radical initiators. Suitable radical initiators include, for example, benzoyl peroxide, Et_3B/O_2, and the like, or most preferably AIBN. Suitable solvents for the carbonyl reduction include MeOH, EtOH, water, benzene, or most preferably toluene. The reaction proceeds at temperatures from 0°C to 110°C.

Referring to Scheme XI below, the indole of apicidin may be subjected to oxidative degradation to prepare carboxylic acid compound **19a** (where R_2 = OH) using conditions known to those skilled in the art.

Scheme XI



19

R_{19} =
19a: $CH_2C(O)R_{19a}$
19b: $C(O)R_{19b}$
19c: $CH_2CH_2OR_{19c}$
19d: CH_2OR_{19d}

R_{19a}, R_{19b}, R_{19c}, and R_{19d} are each independently an alkyl or aryl group, which optionally is substituted.

Suitable oxidants include, but are not restricted to, $KMnO_4$, $KMnO_4/NaIO_4$, $NaIO_4/RuO_4$, and the like, or most preferably $NaIO_4/RuCl_3$. Suitable solvents, or mixtures of solvents include $CHCl_3$, CH_2ClCH_2Cl, MeCN, MeOH, EtOH, *t*BuOH, and the like, or most preferably CH_2Cl_2. The reaction proceeds at temperatures from 0°C to 50°C. This carboxylic acid may be converted into esters or amides as described previously.

Alternatively, a methyl ester may be prepared first (*eg.* compound **19a**, wherein R_{19a} is OMe) and reacted with LiN(OMe)Me, $Me_2AlN(OMe)Me$, or most preferably BrMgN(OMe)Me, to produce a Weinreb amide compound **19a**, in which R_{19a} is N(OMe)Me. Suitable solvents for this reaction include Et_2O, dimethoxyethane, dioxane, and the like, or most preferably THF. The reactions are performed at from -78°C to 50°C and are complete in from 30min to 12h.

Reduction of the sidechain C8-ketone group of compound **19a** to the corresponding alcohol proceeds as described previously. The Weinreb amide thus

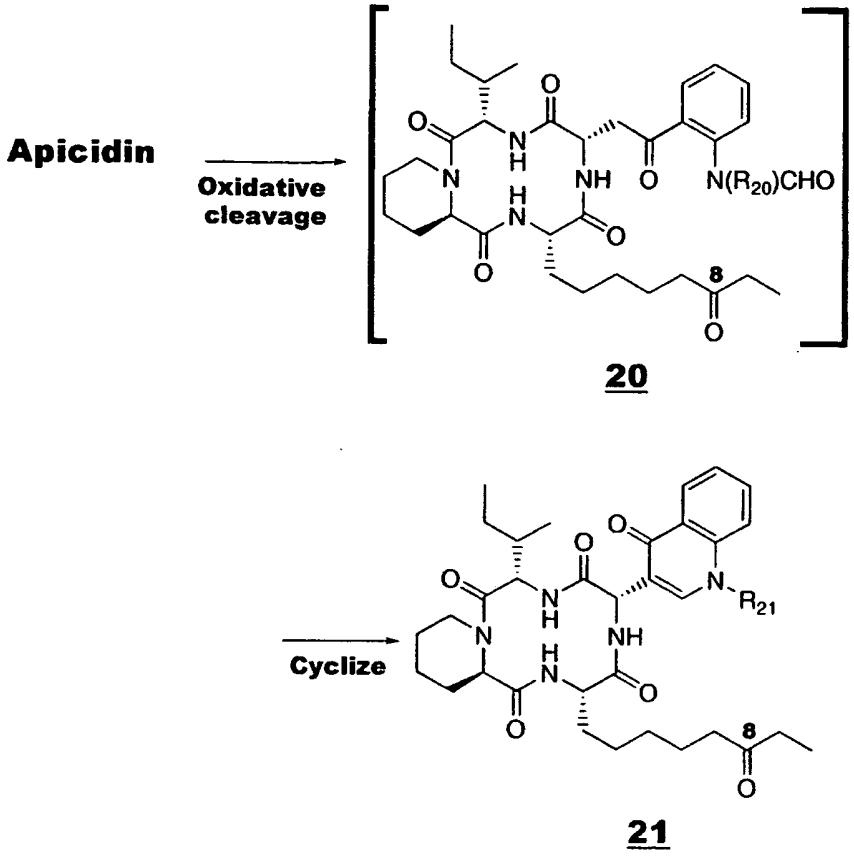
directly generated can then be reacted with hydride reagents, RLi, or RMgX as described previously to prepare the corresponding aldehyde or ketones (*eg.* **19a** where R_{19a} is H, alkyl or aryl group). At this point, the side chain C8-alcohol may be oxidized back to regenerate the C8-ketone as described previously.

When R_{19a} is OH in compound **19a**, the carboxylic acid may be reduced using BH_3 to form an alcohol compound **19c** (where R_{19c} is H). This alcohol may be acylated, sulfonylated or phosphorylated as described previously. Treatment of the alcohol compound **19c** with Ar_3Bi reagents will generate the corresponding aryl ether compound **19c** in which R_{19c} is an aryl group. Both the alpha- and beta-stereoisomers at the tetrapeptide are accessible as described previously.

Substitution of beta-oxo apicidin derivative compound **18** for apicidin in Scheme XI above results in the formation of the truncated apicidin analog compounds **19b** and **19d**.

Referring to Scheme XII, the 2,3-indole bond in Apicidin can be cleaved oxidatively to form compound **20** using conditions known to those skilled in the art.

Scheme XII



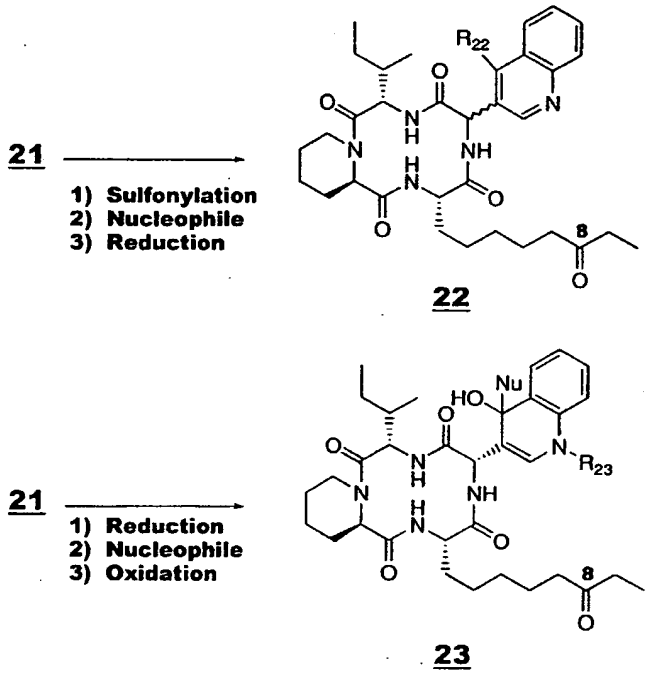
R_{20} and R_{21} are each independently an alkyl or aryl group which optionally is substituted.

Suitable oxidants include $KMnO_4$, $NaIO_4$, $Pb(OAc)_4$, and the like, or more preferably ozone. This reaction may be run in solvents such as $CHCl_3$, CH_2ClCH_2Cl, and the like, or more preferably CH_2Cl_2, at temperatures from -78°C to RT and the reaction is complete in from 1min to 2h. Treatment of compound **20** with a base induces Aldol cyclization to form a quinolone compound **21**. Suitable bases for this reaction include Et_3N, $EtN(iPr)_2$, pyridine, DBU, NaOMe, NaOEt, $NaHCO_3$, and the like, or more preferably $KOtBu$. The Aldol cyclization may be performed in solvents, or mixtures of solvents including CH_2Cl_2, $CHCl_3$, MeOH, EtOH, DMF, THF, Et_2O, DMSO, water, and the like, or more preferably $tBuOH$. The reaction is complete in from 10min to 12h at 0°C to RT. Substitution of N-

substituted-N-desmethoxy-apicidin derivatives (Compound **17**) for apicidin in Scheme XII leads to the formation of N-substituted quinolone derivatives.

Referring to Scheme XIII below, the quinolone compound **21** can be treated with sulfonylating agents as described previously to form compound **22** wherein R_{22} is a sulfonate moiety

Scheme XIII



R_{22} and R_{23} are each independently an alkyl or aryl group, which optionally is substituted.

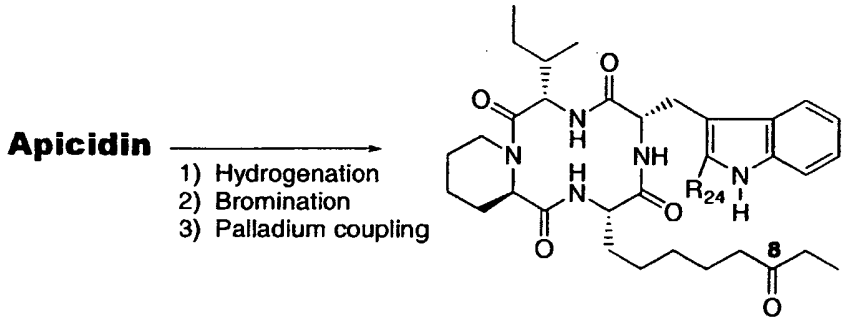
During this reaction, some inversion of stereochemistry at the tetrapeptide ring juncture occurs. When R_{22} of compound **22** is OSO_2CF_3, the triflate can be displaced with suitable nucleophiles, such as halogen, sulfur nucleophiles or nitrogen nucleophiles including, but not limited to, NaBr, NaCl, KI, NaN_3, NaSMe, KSAc, pyridine and the like. The resulting compounds are not shown. Suitable solvents for the displacement reaction include, but are not limited to, CH_2Cl_2, $CHCl_3$, DMF, DMSO, HMPA, NMP, and the like. The reactions proceed at temperatures from 0°C to 80°C.

For apicidin derivative compound **22** in which R_{22} is N-1-pyridinium, the pyridinium group may be reduced using catalytic hydrogenation as described previously.

Further, the C8-ketone group of apicidin derivative compound **21** may be reduced first. The thus formed quinolone carbonyl can then be reacted with nucleophiles such as hydride reagents, RLi or RMgX as described previously. The apicidin derivative compound **23** can be prepared by reoxidation of the C8-alcohol as described previously.

Referring to Scheme XIV below, apicidin may be brominated at the indole C2 position following removal of the N-methoxy group using conditions known to those skilled in the art to form compound **24** where R_{24} is Br.

Scheme XIV



24

Suitable brominating agents include, but are not limited to, Br_2, $Hg(OAc)_2/Br_2$, CBr_4, $CuBr_2$, HOBr, Br_2/HOAc/NaOAc, and the like, or most preferably N-bromosuccinamide. The bromination reaction can be facilitated by a radical initiator such as benzoyl peroxide, Et_3B/O_2 or AIBN.

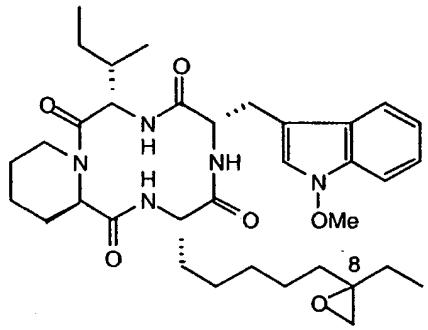
The 2-bromo-indole thus obtained can be further reacted with a palladium catalyst, a base and ArX to induce an aryl coupling reaction. Suitable palladium catalysts include, but are not limited to, $Pd(OAc)_2$, $Pd(OAc)/PPh_3$, $PdCl_2(PPh_3)_2$, $Pd(dba)_2/PPh_3$, and the like, or most preferably $Pd(PPh_3)_4$. Suitable bases for this reaction include, but are not limited to, KO*t*Bu, $CsCO_3$, or most preferably $NaHCO_3$. Suitable solvents, or mixtures of solvent for this coupling reaction include toluene, DMF, MeCN, NMP, DMSO, H_2O, EtOH, or most preferably dioxane/water. Suitable ArX groups include, but are not limited to,

$PhB(OH)_2$, 2-napthylboronic acid, $(4\text{-Me})PhB(OH)_2$, (4-F)PhOTf, and the like. The reactions are complete in from 30min to 48h at temperatures from RT to 110°C.

Synthesis of Side Chain Modified Apicidin Derivatives

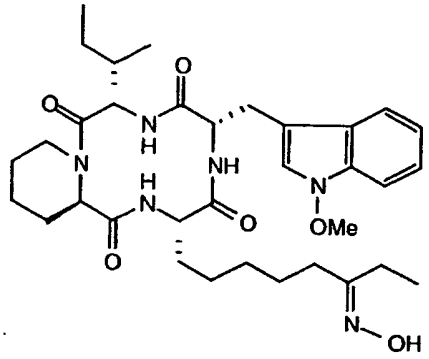
In the Examples, and elsewhere herein, all percentages are by weight unless specifically stated otherwise. Further, all ratios of compounds are by volume unless specifically stated otherwise. Room temperature (RT) means a temperature from about 18°C to about 25°C. If no temperature is specified, then the conditions are understood to be room temperature. In certain steps that describe using an ingredient without specifying an amount, one of ordinary skill would understand the desired result and can determine the amount without difficulty. In general, the purities of the pure Examples were better than about 95% pure.

EXAMPLE 1



Example 1 was prepared by the following procedure. At room temperature, 27mg of $Me_3S(O)I$ was added to a mixture of i) 5.6mg of 60% NaH and ii) 0.35mL HMPA. The resulting solution was allowed to stand for 5min. Then, a mixture of 12mg apicidin in 96µL DMF was added to form a reacting mixture. After 48 hours, the reaction was quenched with water, extracted with EtOAc and dried in Na_2SO_4 to produce 8mg Example 1. Example 1 was thus obtained without requiring further purification and was characterized by ^1H NMR and MS [m/z: 638 (M^++1)].

EXAMPLE 2



Example 2 was prepared by the following procedure. At room temperature, 60mg $HCl•H_2NOH$ and 181μL Et_3N was added to 20mg apicidin in 10mL CH_2Cl_2. The resulting solution was aged for 12h. The volatiles were then removed under reduced pressure. Example 2 was obtained following preparative RP-HPLC (reversed phase high performance liquid chromatography), without workup, using a gradient elution characterized by 1:3 MeCN:H_2O to 100% MeCN, with a 60min linear ramp. The pure Example 2 thus obtained was characterized by ^1H NMR and MS [m/z: 639.3 (M^++1)].

EXAMPLES 3A-3M

Examples 3a-3m were prepared following the general procedure described in Scheme III for compound 11f, 11g, and 11h, and for Ex.2. Examples 3a-3m are described by the following chemical formula and were characterized by NMR and mass spectroscopy:

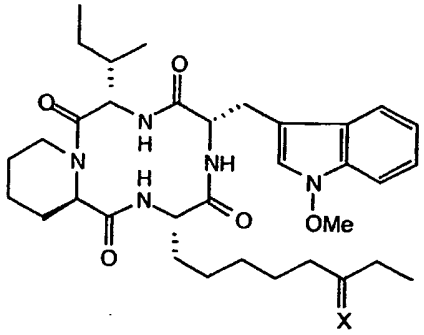
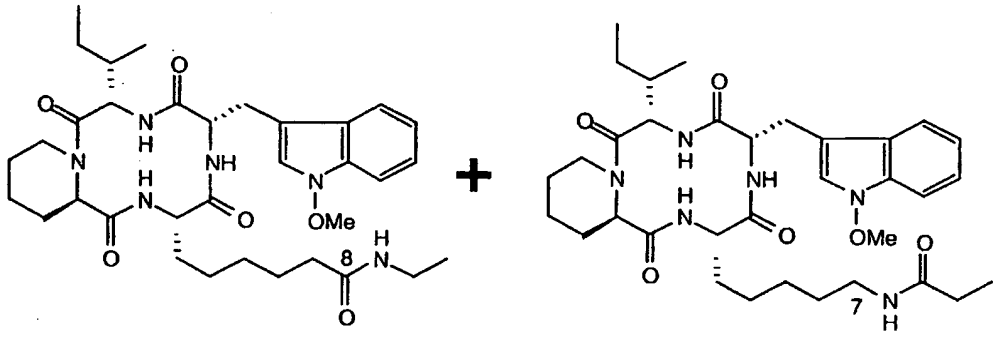


Table 1

Example	X Group	Mass Spec
Ex. 3a	$NNHSO_2Ph(4\text{-}Me)$	-----
Ex. 3b	$NOCH_2Ph$	729.2 (M^++1)
Ex. 3c	NNH-Dansyl	871.2 (M^++1)
Ex. 3d	$NOCH_2CO_2$-Na+	-----
Ex. 3e	$NOCH_2CO_2H$	697.2 (M^++1)
Ex. 3f	NOMe	653.2 (M^++1)
Ex. 3g	NNH-Texas Red	1227.2 (M^++1)
Ex. 3h	$NOCH_2C(O)NHCH_2CH_2OH$	-----
Ex. 3i	$NOCH_2C(O)$(N-1-pyrrolindinyl)	-----
Ex. 3j	$NOCH_2CO_2Me$	-----
Ex. 3k	NOC(O)Ph	-----
Ex. 3l	NOC(O)Me	-----
Ex. 3m	NOC(O)*t*Bu	-----

EXAMPLES 4A AND 4B

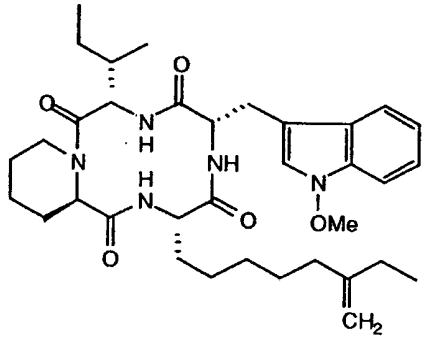


Ex. 4a **Ex. 4b**

Examples 4a and 4b were prepared by the following procedure. At 0°C, 4.5mg of *p*-toluenesulfonyl chloride was added to 3mg of Example 2 (the C8-ketoxime of apicidin) in 0.5mL pyridine to form a solution. The solution was

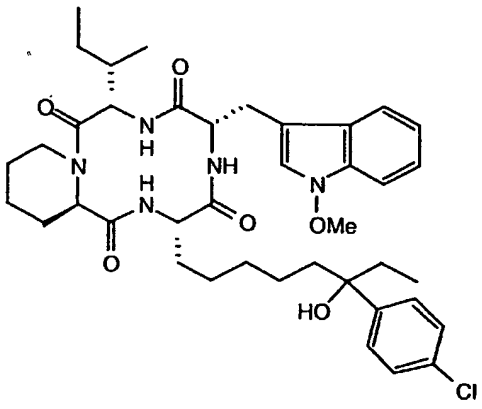
maintained at 0°C for 10min, then warmed to RT and aged for 50min. Then 1mL each of saturated brine and saturated $NaHCO_3$(aq) were added. Next, the solution was extracted with EtOAc and dried with Na_2SO_4. A mixture of pure Examples 4a and 4b was obtained following preparative RP-HPLC using gradient elution (1:3 MeCN:H_2O isocratic for 10min, then a 75min linear ramp to 100% MeCN). The pure mixture thus obtained was characterized by ^1H NMR and MS [m/z: 639.2 (M^++1)].

EXAMPLE 5



Example 5 was prepared by the following procedure. At room temperature (RT), 114mg of $Ph_3PCH_3^+Br^-$ was added to i) 16.8mg of a 60% dispersion of NaH in oil, ii) 2mL DMF, and iii) 0.2mL HMPA to form a mixture. After the mixture ceased foaming, a solution of 20mg apicidin in 1mL DMF was added. The resulting solution was aged for 4 hours. Preparative RP-HPLC without workup using gradient elution (1:3 MeCN:H_2O isocratic for 10min, then a 75min linear ramp to 100% MeCN yielded 14mg of pure Example 5 which was characterized by ^1H NMR and MS [m/z: 622.3 (M^++1)].

EXAMPLES 6A-6D



Ex. 6a

Example 6a was prepared by the following procedure. At 0°C, 0.12mL of 1.0M (4-Cl)PhMgBr in Et_2O was dropwise added to 15mg apicidin in a mixture of 1.75mL THF and 0.25mL pyridine. After 1h at 0°C, an additional 0.12mL of 1.0M (4-Cl)PhMgBr in Et_2O was added. The resulting solution was aged for 1h at 0°C and then 1h at RT. The reaction was quenched by the addition of saturated NH_4Cl(aq) to the solution. The quenched mixture was extracted with EtOAc and dried with Na_2SO_4. Preparative RP-HPLC using gradient elution (1:3 MeCN:H_2O isocratic for 10min, then a 75min linear ramp to 100% MeCN) yielded 8mg of pure Example 6a, which was characterized by ^1H NMR and MS [m/z: 736.3 (M^++1)].

Examples 6b, 6c, and 6d are described by the chemical structure shown below. The specific substituents are tabulated in Table 2. Examples 6b, 6c, and 6d were prepared following the general procedure described in Scheme III for compound **11b** under conditions similar to those described above for Ex. 6a

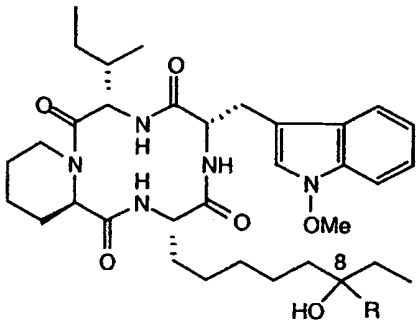
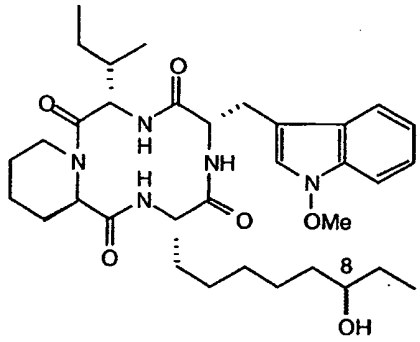


Table 2

Example	R Group	Mass Spec
Ex. 6b	CH_2Ph	716.4 (M^++1)
Ex. 6c	C_6H_{11}	708.4 (M^++1)
Ex. 6d	CH_2CH_3	654.4 (M^++1)

EXAMPLE 7

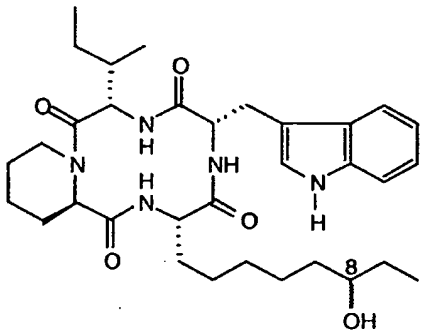
cyclo(N-O-Methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-hydroxy-decanoyl)



Example 7 was made by first adding 18mg $NaBH_4$ to 300mg apicidin in 12mL MeOH at 0°C. Next, the ice bath was removed immediately and the solution was stirred at RT for 4 hours. Acetone was added to quench the reaction and the solvents were removed under reduced pressure at ambient temperature. The residue was dissolved in CH_2Cl_2, poured into saturated $NaHCO_3$, extracted with 1:9 *i*PrOH:CH_2Cl_2 and dried with Na_2SO_4. The pure product was obtained following

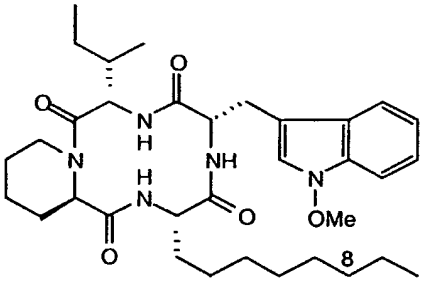
flash chromatography on silica gel using 1:1 acetone:hexanes as eluant. The pure Example 7 was characterized by ^{1}H NMR. TLC: R_f = 0.32 (1:1 acetone:hexanes).

EXAMPLE 8



Example 8 was prepared following the general procedure of Example 7 but using N-desmethoxy-apicidin as the starting material. Example 8 was characterized by ^{1}H NMR and MS [m/z: 596 (M^++1)].

EXAMPLE 9

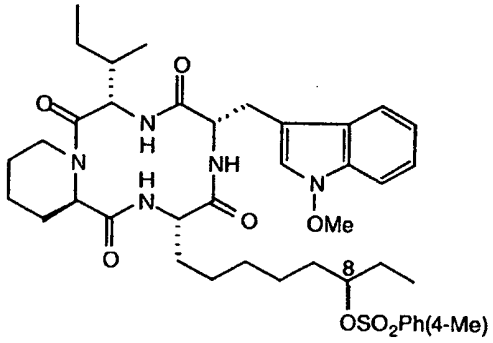


Example 9 was prepared by the following process. At room temperature, 57mg of thiocarbonylimidazole was added to 40mg of *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-hydroxy-decanoyl) in 1.6mL CH_2Cl_2. The resulting solution was heated to 75°C for 2 hours. Next, 1mg of DMAP (4-dimethylaminopyridine) was added and the solution aged for 1h at 75°C and 48h at RT. The solvent then was removed under reduced pressure. 59mg of the pure intermediary product 8-OC(S)imidazolyl-apicidin (also known as *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-imidazoylylthionooxy-decanoyl) was obtained by

PTLC (2 x 1500μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant and was characterized by ^1H NMR and MS [m/z: 736 (M^++1)].

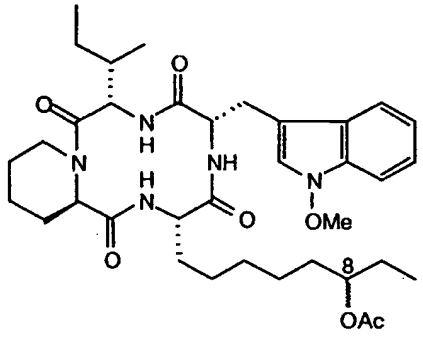
To the above prepared 59mg of intermediary product 8-OC(S)imidazolyl-apicidin in 1.6mL toluene was added 2.6mg AIBN and 53μL *n*Bu3SnH. The solution was then degassed and heated to 80°C for 1h, concentrated under reduced pressure, and partitioned between MeCN and hexanes. The hexanes layer was discarded. The volatiles were removed under reduced pressure and pure Example 9 product was obtained following RP-HPLC using gradient elution (4:6 to 1:0 MeCN:H_2O). Example 9 was characterized by ^1H NMR and MS [m/z: 610 (M^++1)].

EXAMPLE 10



Example 10 was made by adding 10mg DMAP to 100mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-hydroxy-decanoyl) in 2mL pyridine at RT. Next, 94mg tosic anhydride was added. After 3d at RT, the solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Pure Example 10 was obtained following flash chromatography on silica gel using gradient elution (1:1:98 then 1:2:97 then 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant). Example 10 was characterized by ^1H NMR. TLC: R_f = 0.36 (1:3:96 NH_4OH:MeOH:$CHCl_3$).

EXAMPLE 11



The procedure to form Example 11 was as follows. At room temperature, 50mg $NaBH_4$ was added to 100mg apicidin in 10mL 1:1 THF:MeOH. After 30min at RT, the solution was poured into brine, extracted with CH_2Cl_2 and dried with Na_2SO_4. To the residue thus obtained was added 2mL pyridine, followed by addition of 10mg DMAP and 10 drops of Ac_2O. After another 15min at RT, the solution was heated to 80°C for 10min. without noting any reaction. An additional 5 drops of fresh Ac_2O (from an unopened bottle) were added and the solution stirred at RT for 24 hours. The solvents were removed under reduced pressure and the residue was lyophilized from dioxane. Preparative RP-HPLC using gradient elution (3:7 to 6:4 MeCN:H_2O) yielded 69mg of pure Example 11 product, which was characterized by ^1H NMR and MS [m/z: 668.6 (M^++1)]. HPLC: t_R = 4.95min (6:4 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8 available from Rainin Co.

EXAMPLES 12A-12E

Following the general procedure described in Scheme III, compounds 11c and 11d, and similarly to the procedure for Examples 10 and 11, the following Examples 12a-12f were prepared and characterized by NMR and mass spectroscopy:

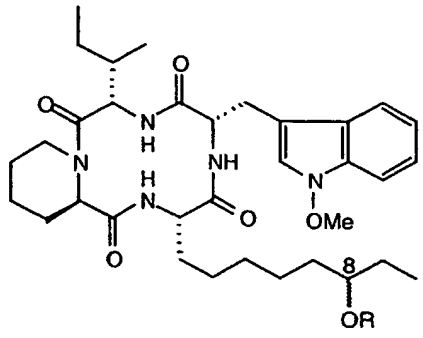
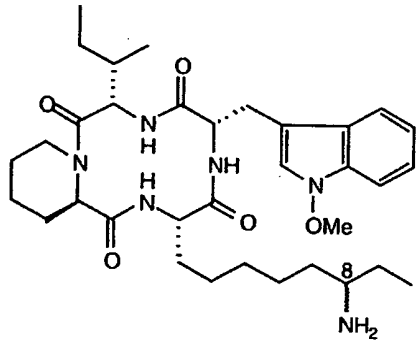


Table 3

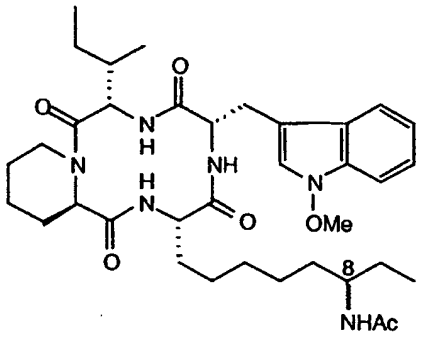
Example	R Group
12a	C(O)Ph
12b	C(O)*t*Bu
12c	C(O)Ph(F_5)
12d	SO_2Me
12e	$SO_2Ph(4\text{-}NO_2)$
10	$SO_2Ph(4\text{-}Me)$

EXAMPLE 13



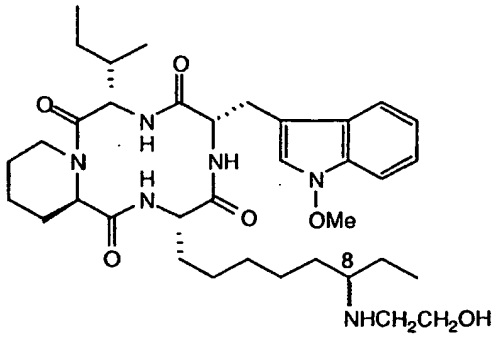
To form Example 13, 0.16mL $(Me_3Si)_2NH$ and 235mg $ZnCl_2$ was added to 100mg apicidin in 5mL EtOAc at RT. The solution was heated to 55°C for 12 hours. The solution was then cooled to 0°C and 12mg $NaBH_4$ was added. After 1h, the solution was warmed to RT and aged an additional 2h. The solution was poured into 1:1 brine:saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Pure Example 13 product was obtained following preparative RP-HPLC using gradient elution (3:7 to 6:4 MeCN:H_20) and was characterized by ^1H NMR and MS [m/z: 625.3 (M^++1)]. TLC: R_f= 0.22min (1:9:90 NH_4OH:MeOH:$CHCl_3$).

EXAMPLE 14



To form Example 14, 2 drops Ac_2O and a catalytic amount of DMAP was added to 14mg 8-amino-8-desoxo apicidin in 2mL pyridine at 0°C. The solution was stirred at 0°C for 30min and at RT for another 30min. Next, 1mL methanol was added and the solution was then concentrated under reduced pressure. Pure Example 14 was obtained following preparative RP-HPLC purification (gradient elution using 25:75 MeCN:H_2O for 10min, then a 70min ramp to 100% MeCN) and was characterized by ^1H NMR and MS [m/z: 667.4 (M^++1)]. TLC: R_f = 0.67 (1:9:90 NH_4OH:MeOH:$CHCl_3$). HPLC: t_R = 4.60min, 1:1 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

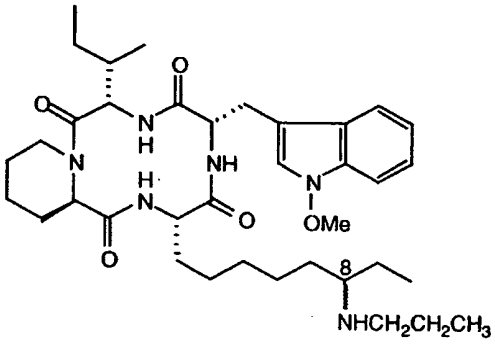
EXAMPLE 15



Example 15 was made by first adding to 60mg apicidin in 0.5mL MeOH at RT i) 1mL pyridine, ii) 40µL ethanolamine, iii) 60µL glacial HOAc (pH ~ 5.0), and iv) powdered 4Å sieves. The solution was cooled to 0°C and 7.9mg $NaCNBH_3$ was added. After 2h, the solution was warmed to RT and aged for 12h. The solution was then filtered through Celite filter agent (available from Aldrich

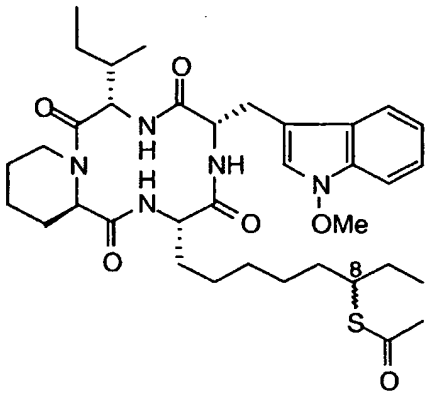
Chemical Company, Milwaukee, Wisconsin) using 1:1 CH_2Cl_2:MeOH as eluant, reduced in volume *in vacuo*, poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following preparative RP-HPLC using 1:1 MeCN:H_2O to 100% MeCN gradient elution, 4.2mg pure Example 15 was obtained. The product thus obtained was characterized by ^1H NMR and MS [m/z: 669 (M^++1)].

EXAMPLE 16



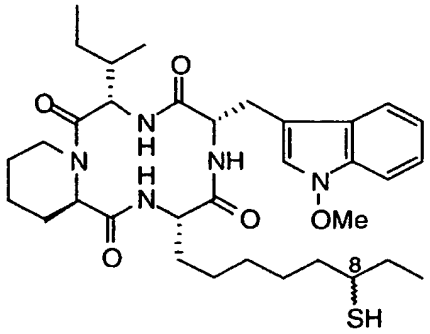
Example 16 was prepared similarly to Example 15. At room temperature, to 60mg apicidin in 0.5mL MeOH was added i) 2mL pyridine, ii) 0.5mL propylamine, iii) 1mL glacial HOAc (pH ~ 4.5), and iv) powdered 4Å sieves. The solution was cooled to 0°C and 60mg $NaCNBH_3$ was added. After 2h, the solution was warmed to RT and aged for 12h. The solution was filtered through Celite using 1:1 CH_2Cl_2:MeOH as eluant, reduced in volume *in vacuo*, poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Pure Example 16 was obtained following PTLC on silica gel (1 x 1500μm plate) using 2:18:80 NH_4OH:MeOH:$CHCl_3$ as eluant. The pure Example 16 product thus obtained was characterized by ^1H NMR and MS [m/z: 667 (M^++1)].

EXAMPLE 17



To form Example 17, 32mg KSAc was added to 18.1mg of the Example 10 C8-tosylate compound in 3mL 95% EtOH. The solution was heated to 70°C for 3 hours. The solution was then cooled to RT and saturated NH_4Cl(aq) was added. Next, the solution was extracted with EtOAc and dried with Na_2SO_4. The solution then was filtered, evaporated to dryness. PTLC on silica gel (1 x 1000μm plate) using 3:7 acetone:hexanes as eluant yielded 3.4mg of pure Example 17 product that was characterized by ^{1}H NMR.

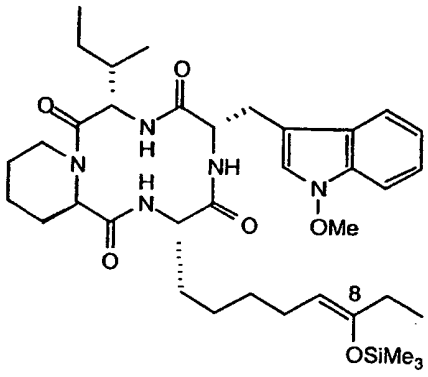
EXAMPLE 18



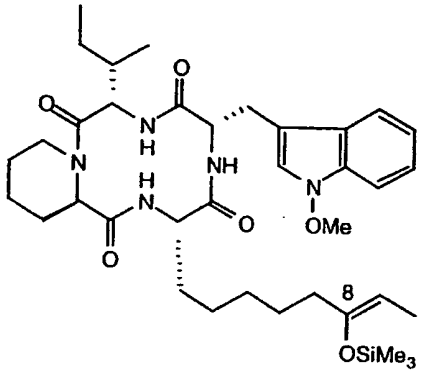
To form Example 18, 3.4mg of the Example 17 C8-thioacetate compound was placed at RT in 0.2mL NaOMe 2M solution in MeOH) and aged for 3h. The solution was poured into saturated NH_4Cl(aq), extracted with CH_2Cl_2, and dried with Na_2SO_4. The solution was filtered, concentrated to dryness, and pure

Example 18 was obtained following RP-HPLC. Example 18 thus obtained was characterized by ^{1}H NMR.

EXAMPLES 19A AND 19B



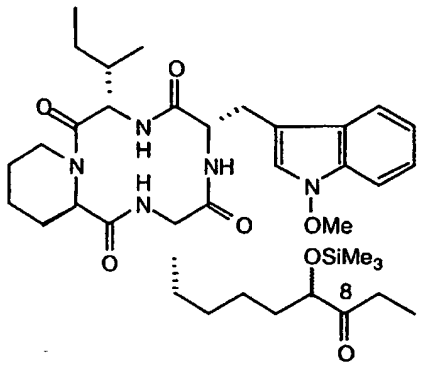
Ex. 19a



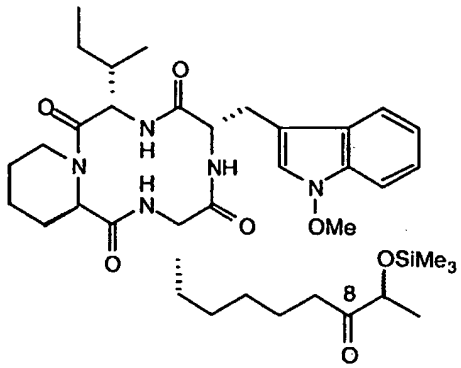
Ex. 19b

Examples 19a and 19b were prepared by the following procedure. 50mg apicidin was heated in 5mL THF at 50°C until the resulting solution became homogenous. The solution was then cooled to -78°C and immediately 800μL 0.5M potassium hexamethyldisilazane in toluene was added. After 5min, 40L TMSCl as a solution in 1mL THF was added. After 10min at -78°C the reaction was stopped by the addition of 5mL saturated $NaHCO_3$. Next, the solution was extracted, first with EtOAc, followed by CH_2Cl_2 and dried with Na_2SO_4. The crude mixture of Example 19a and Example 19b was used with no further purification in the next reaction. The crude yield was 74mg (145%). The mixture was characterized by ^{1}H NMR. TLC: $R_f = 0.52$ (1:2 acetone:hexanes).

EXAMPLES 20A AND 20B



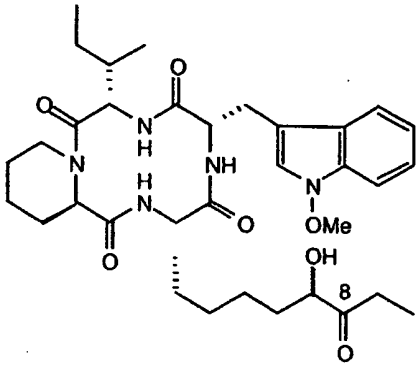
Ex. 20a



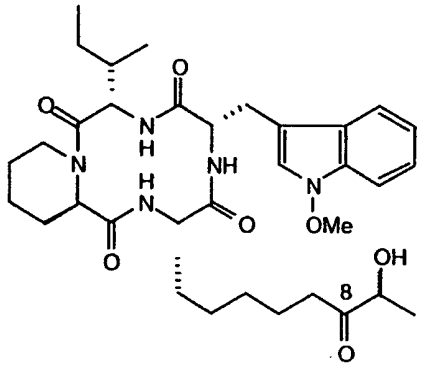
Ex. 20b

To form Examples 20a and 20b, 74mg of the crude ~1:1 mixture Example 19a, *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-trimethylsiloxy-7-ene- decanoyl), and Example 19b, *cyclo*(N-O-Methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-trimethylsiloxy-8-ene-decanoyl), was placed in 5mL CH_2Cl_2 at RT to which was added 200mg solid $NaHCO_3$. To this solution was added 20mg 85% MCPBA. After 5min, the reaction was quenched with 1:1 saturated $Na_2S_2O_3$:saturated $NaHCO_3$, extracted with CH_2Cl_2, and dried with Na_2SO_4. This yielded a 43mg pure mixture of Example 20a, *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-7-trimethylsiloxy-decanoyl), and Example 20b, *cyclo*(N-O-Methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-9-trimethylsiloxy-decanoyl) following flash chromatography on silica gel using 4:1 hexanes:acetone as eluant. The mixture was characterized by ^1H NMR. TLC: $R_f = 0.33$ (1:2 acetone:hexanes).

EXAMPLES 21A AND 21B



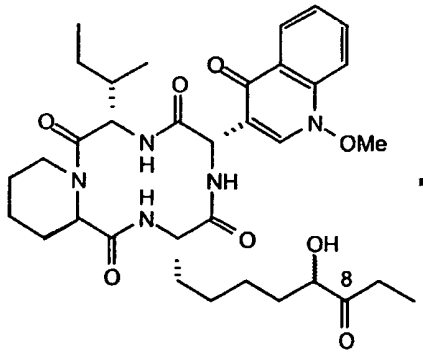
Ex. 21a



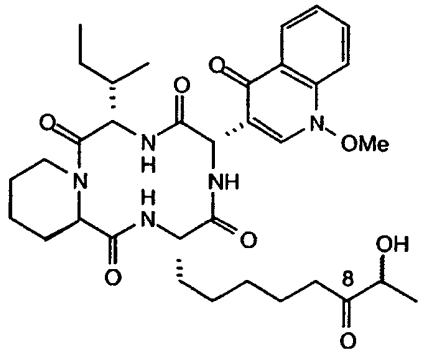
Ex. 21b

Example 21a and Example 21b were prepared by the following procedure. To 43mg of a 1:1 mixture of Example 20a, *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-7-trimethylsiloxy-decanoyl), and Example 20b, *cyclo*(N-O-Methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-9-trimethylsiloxy-decanoyl), in 4mL THF at RT was added 120µL 1M *n*Bu4NF in THF. After 20min at RT, the solvent was evaporated under reduced pressure and the crude mixture purified by RP-HPLC without workup using 6:4 MeCN:H_2O. The resulting pure mixture of Examples 21a and 21b was characterized by ^{1}H NMR and MS [m/z: 657.2 (M^++NH_4)]. TLC: R_f = 0.14 (1:2 acetone:hexanes).

EXAMPLES 22A AND 22B



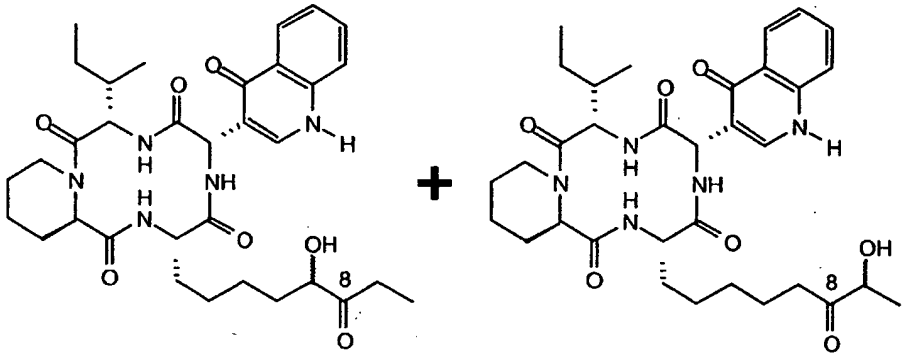
Ex. 22a



Ex. 22b

Following the general procedure of Examples 19-21, a 95% pure mixture of Examples 22a and 22b was prepared and characterized by ^{1}H NMR.

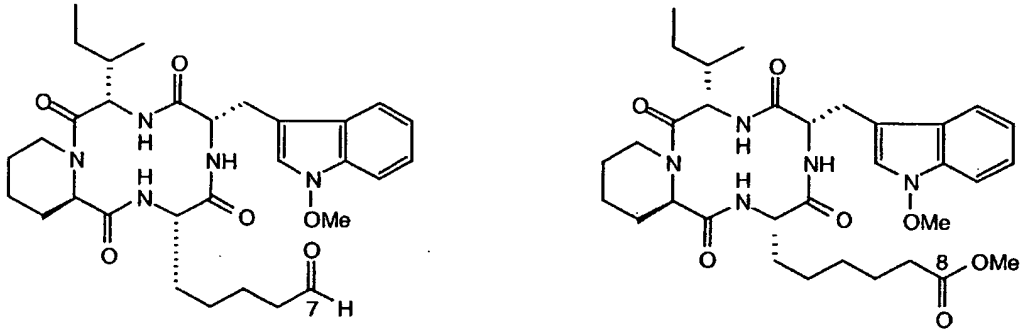
EXAMPLES 23A AND 23B



Ex. 23a **Ex. 23b**

Following the general procedure of Examples 19-21, a 95% pure mixture of Example 23a and 23b was prepared and characterized by ^{1}H NMR.

EXAMPLES 24A AND 24B



Ex. 24a **Ex. 24b**

Examples 24a and 24b were prepared by adding 10mL pyridine to 10mg ~1:1 mixture of Examples 21a and 21b in 3mL MeOH at 0 °C, followed by the addition of 10mg $Pb(OAc)_4$. After 10min, the solution was quenched with 2mL $Na_2S_2O_3$, diluted with about 2mL brine, extracted with CH_2Cl_2 and dried with

Na_2SO_4. Following preparative TLC on silica gel (500μm plate) using 1:2 acetone:hexanes as eluant, separated pure products were obtained.

Example 24a, *cyclo*(N-O-Methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-oxo-heptanoyl) (5.5mg) was characterized by ^{1}H NMR and MS [m/z: 582.2 (M+1)]. TLC: R_f = 0.16 (1:2 acetone:hexanes).

Example 24b, *cyclo*(N-O-Methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-carboxymethyl-heptanoyl) (6.5mg) was characterized by ^{1}H NMR and MS [m/z: 626.3 (M^++1)]. TLC: R_f = 0.23 (1:2 acetone:hexanes).

EXAMPLES 25A-25D

Examples 25a-25d were prepared by following the general procedure of Example 24b. Starting with Examples 21a and 21b, and using an appropriate alcohol as solvent, the following derivatives were prepared and analyzed by NMR and mass spectroscopy:

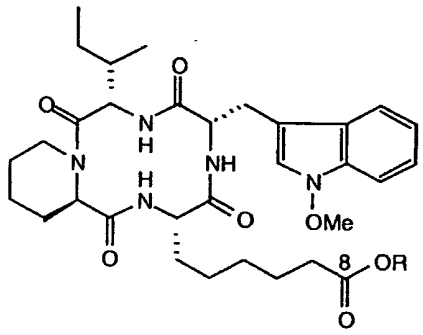
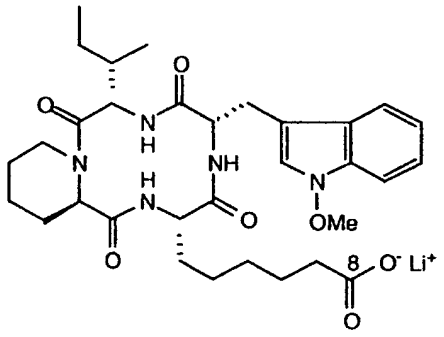


Table 4

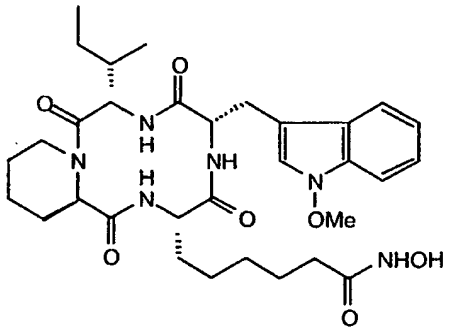
Example	R Group	Mass Spec
25a	Et	640.5 (M^++1)
25b	*n*Pr	654.4 (M^++1)
25c	*n*Bu	668.3 (M^++1)
25d	*i*Pr	654.4 (M^++1)

EXAMPLE 26



Example 26 was prepared by the following procedure. To 41mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-carbomethoxy-heptanoyl) in 4mL 3:1:1 THF:MeOH:H_2O at 0°C was added 100μL 1M LiOH. The solution was stirred for 1h and then additional 300μL 1M LiOH was added. After 12h, 33mg pure Example 26 product was obtained following preparative RP-HPLC without workup using gradient elution (column equilibrated in 5:95 MeCN:H_2O, using 25:75 MeCN:H_2O for 40min followed by a 20min ramp to 100% MeCN, flow rate 10mL/min). Example 26 was characterized by ^{1}H NMR and MS [m/z: 629.2 (M^++NH_4)]. HPLC: t_R = 1.98min 45:55 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

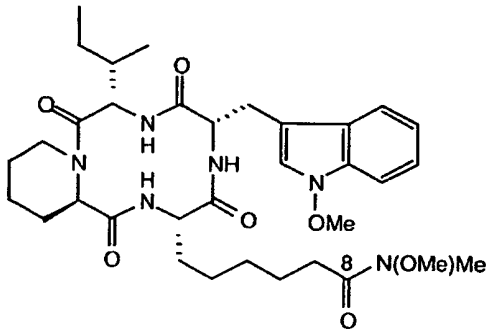
EXAMPLE 27



Example 27 was prepared by the following procedure. To 15mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-carboxy-heptanoyl), lithium salt in 3mL DMF at RT was added 5.4mg $H_2NOSi(Me)_2tBu$ and 7mg EDC•HCl. After 2h at RT, 15mg additional $H_2NOSi(Me)_2tBu$ (15mg) and 14mg EDC•HCl were added and the solution allowed to stir overnight. The reaction was quenched by the addition

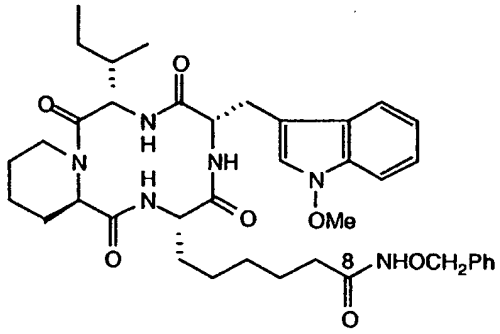
of 5 drops glacial HOAc and 1mL MeOH. The solution was poured into brine, extracted with CH_2Cl_2, and dried with Na_2SO_4. The crude product was chromatographed on silica gel using gradient elution (1:3:96 NH_4OH:MeOH:$CHCl_3$ to 1:4:95 NH_4OH:MeOH:$CHCl_3$, to 1:9:90 NH_4OH:MeOH:$CHCl_3$). To remove some contaminating EDU present in the chromatographed material, the product was dissolved in 2mL $CHCl_3$ and 2mL 10% aq. HOAc. After 5min, the aqueous layer was decanted and the washing repeated twice more to yield 5.5mg pure Example 27 product. The pure Example 27 stained positive (purple-orange) for a hydroxamic acid using $Fe^{(III)}Cl_3$ stain. The product was characterized by ^{1}H NMR and MS [m/z: 627.3 (M^++1)]. TLC: R_f = 0.26 (then 1:9:90 NH_4OH:MeOH:$CHCl_3$).

EXAMPLE 28



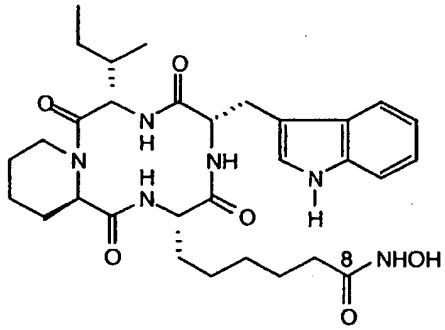
Example 28 was prepared by the following procedure. To 30mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-carboxy-heptanoyl) lithium salt in 1mL DMF at RT was added 47mg HCl•HN(OMe)Me, 2mg DMAP, 7mg HOBT (1-hydroxybenzotriazole hydrate) and 90µL DIEA (Et_2NiPr) followed by 12mg EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride). After 36h, the solution was poured into brine, acidified to pH~4.0 with 2N HCl, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following flash chromatography on silica gel using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, 29.6mg purified Example 28 was obtained and was characterized by ^{1}H NMR and MS [m/z: 655.3 (M^++1)]. TLC: R_f = 0.39 (1:3:96 NH_4OH:MeOH:$CHCl_3$). HPLC: t_R = 3.90min (62:38 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

EXAMPLE 29



Example 29 was prepared by the following procedure. To 150mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-carboxy-heptanoyl) in 14mL CH_2Cl_2 at 0°C was added 78mg $HCl \cdot H_2NOCH_2Ph$, 0.13mL DIEA, 33mg HOBT, 2mg DMAP, and 108mg BOP. After 1h at 0°C and 12h at RT, the solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following preparative TLC on silica gel (5 x 1000μm plates) using 5:95 MeOH:$CHCl_3$ as eluant, 137mg pure Example 29 was obtained and was characterized by ^1H NMR. TLC: $R_f = 0.62$ (5:95 MeOH:$CHCl_3$). HPLC: $t_R = 7.46$min (45:55 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

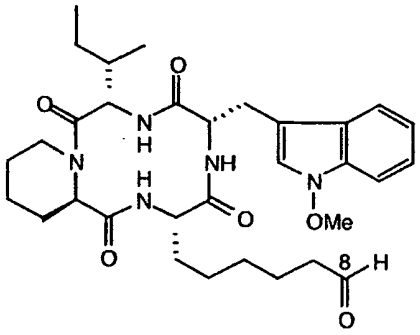
EXAMPLE 30



Example 30 was prepared by the following procedure. To 130mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-(N-benzyloxy-carboxamido)-heptanoyl) in 5mL MeOH at RT was added 5% Pd/C and an H_2 atmosphere (balloon pressure) was established. After 12h, 10mg $Pd(OH)_2$ was added and the reaction continued for an additional 2h. The catalyst was removed by filtration through Celite

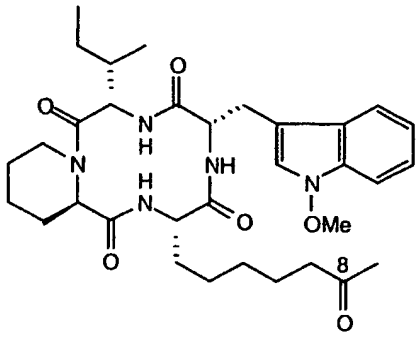
using MeOH as eluant and the solution concentrated under reduced pressure. Pure Example 30 product was obtained following RP-HPLC purification using gradient elution (5:95 MeCN:H_2O for 5min then 55min ramp to 50:50 MeCN:H_2O). The pure Example 30 was characterized by ^1H NMR and MS [m/z: 597.5 (M^++1)]. TLC: R_f = 0.11 (1:9:90 NH_4OH:MeOH:$CHCl_3$). HPLC: t_R = 10.65min (2min ramp from 5:95 MeCN:H_2O to 1:1 MeCN:H_2O, 1.0mL/min, Zorbax™ RX-8).

EXAMPLE 31



Example 31 was prepared by the following procedure. To 10mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-(N-O-methyl-N-methyl-carboxamido)-heptanoyl) in 2mL THF at 0°C was added 150μL 1M CH_2=CHMgBr in Et_2O. After 15min at 0°C, the solution was cooled to -78°C and quenched by addition of 1mL saturated NH_4Cl. The solution was poured into brine and extracted with CH_2Cl_2 and dried with Na_2SO_4. The product was partially purified on a silica gel pipette plug using 1:2 acetone:hexanes as eluant. Following preparative TLC on silica gel (1 x 250μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, 2.1mg pure Example 31 was obtained and was characterized by ^1H NMR and MS [m/z: 596.3 (M^++1)]. TLC: R_f = 0.57 (1:3:96 NH_4OH:MeOH:$CHCl_3$).

EXAMPLE 32



Example 32 was prepared by the following procedure. To 7mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-(N-methoxy-N-methyl-carboxamido)-heptanoyl) in 1mL THF at 0°C was added 55μL 1M MeMgBr in Et_2O. After 10min, an additional 55μL 1M MeMgBr in Et_2O was added. The solution was poured into saturated NH_4Cl, extracted with CH_2Cl_2 and dried with Na_2SO_4. 4.3mg pure Example 32 product was obtained following preparative TLC on silica gel (1 x 500μm plate) using 4:6 acetone:hexanes as eluant. The pure Example 32 was characterized by ^1H NMR and MS [m/z: 610.3 (M^++1)]. TLC: R_f = 0.22 (1:2 acetone:hexanes). HPLC: t_R = 4.51 min (1:1 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

EXAMPLES 33A-33C

Following the general procedure illustrated in Example 26-34, the following derivatives were prepared:

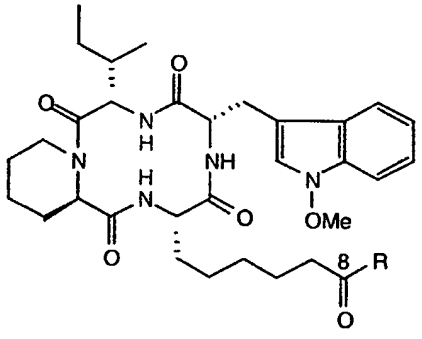
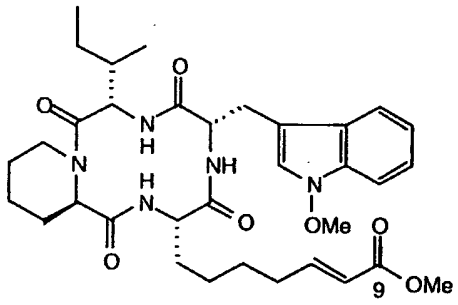


Table 5

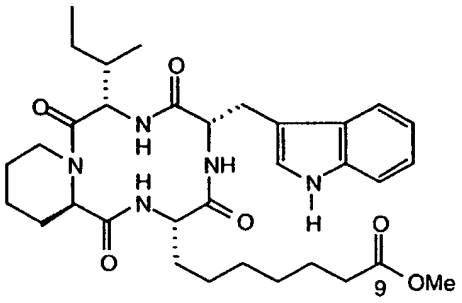
Example	R Group	Mass Spec
32	Me	610.3 (M^++1)
33a	*n*Pr	638.5 (M^++1)
33b	*i*Pr	638.5 (M^++1)
33c	Ph	672.5 (M^++1)

EXAMPLE 34



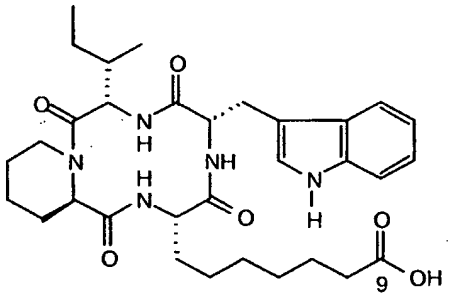
Example 34 was prepared by the following procedure. To 25mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-oxo-heptanoyl), 11mg anhydrous LiCl, and 21mL $(MeO)_2P(O)CH_2CO_2Me$ in 2.5mL MeCN at RT, was added 42mL DIEA. After 2h the solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Pure Example 34 product was obtained following flash chromatography on silica gel using 1:2 acetone:hexanes as eluant. The pure Example 34 was characterized by ^1H NMR and MS [m/z: 638.2 (M^++1)]. TLC: R_f = 0.38 (1:2 acetone:hexanes). HPLC: t_R = 5.09min, (1:1 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

EXAMPLE 35



Example 35 was prepared by the following procedure. To 35mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7,8-dehydro-8-carbomethoxy-octanoyl) in 4mL 1:1 THF:MeOH was added 20mg $Pd(OH)_2$ and an H_2 atmosphere (balloon pressure) was established. After 12h, the catalyst was filtered off and 11.7mg pure Example 35 product was obtained following flash chromatography on silica gel using 1:2 acetone:hexanes as eluant. The pure Example 35 was characterized by ^1H NMR. TLC: $R_f = 0.21$ (1:2 acetone:hexanes). HPLC: $t_R = 3.84$min (55:45 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

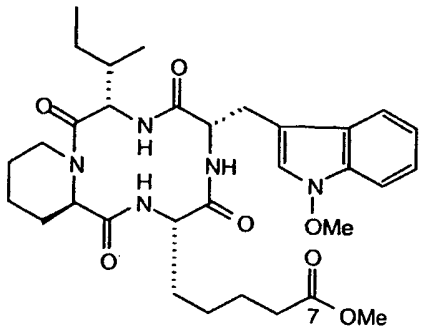
EXAMPLE 36



Example 36 was prepared by the following procedure. To 10.6mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-carbomethoxy-octanoyl) in 1mL 3:1:1 THF:MeOH:H_2O at 0°C was added 15mL 1M LiOH. The solution was stirred for 1h at 0°C, 6h at RT, 3 days at 4°C and then an additional 30mL 1M LiOH was added. After 8h longer, the solvents were removed using a vigorous stream of N_2 and pure Example 36 product was obtained by purification without workup using preparative RP-HPLC (gradient elution using 2:8 MeCN:H_2O for 10min followed by

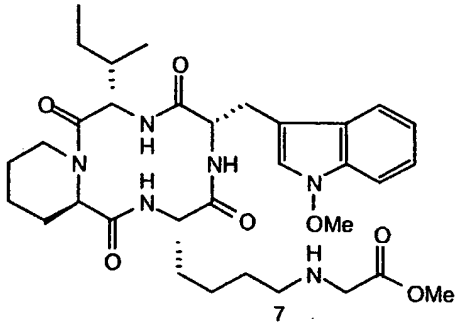
a 60min ramp to 100% MeCN). Pure product was characterized by ^{1}H NMR and MS [m/z: 596.3 (M^++1)]. HPLC: t_R = 2.89min (3:7 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

EXAMPLE 37



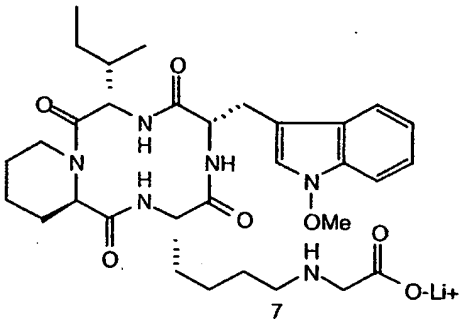
Example 37 was prepared by the following procedure. To 25mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-oxo-heptanoyl) in 1.25mL DMF at RT was added 0.25mL MeOH followed by 67.5mg PDC. The solution was stirred for 3.5h and then filtered through 1" silica gel, with 0.5" Celite on top of it, using MeOH as eluant. The solvents were removed under reduced pressure. Pure 9mg Example 37 product was obtained following preparative TLC on silica gel (2 x 1000μm plates) using 5:95 MeOH:$CHCl_3$ as eluant. The pure Example 37 was characterized by ^{1}H NMR and MS [m/z: 612.3 (M^++1)]. TLC: R_f = 0.24 (1:2 acetone:hexanes). HPLC: t_R = 9.41min (45:55 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

EXAMPLE 38



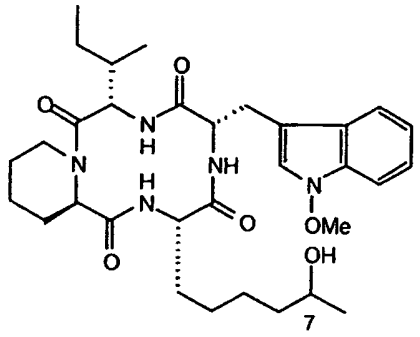
Example 38 was prepared by following the general procedure of Example 15, and Scheme III, utilizing methyl glycinate in place of ethylamine, and was characterized by ^{1}H NMR and MS [m/z: 655.0 (M^++1)].

EXAMPLE 39



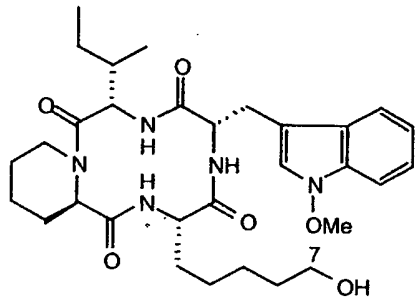
Example 39 was prepared by following the general procedure of Example 36 and starting with the methyl ester of Example 38, and was characterized by ^{1}H NMR and MS [m/z: 641.4 (M^++1)].

EXAMPLE 40



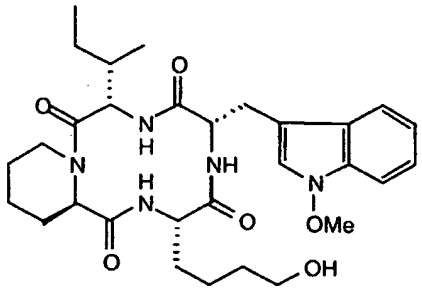
Example 40 was prepared by following the general procedure of Example 7, utilizing Example 32 as the starting material, and was characterized by ^1H NMR and MS [m/z: 598.3 (M^++1)].

EXAMPLE 41



Example 41 was prepared by following the general procedure of Example 7 to convert the C7-aldehyde of Example 23 and was characterized by ^1H NMR and MS [m/z: 584.2 (M^++1)].

EXAMPLE 42



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Example 42 was prepared by the following two methods.

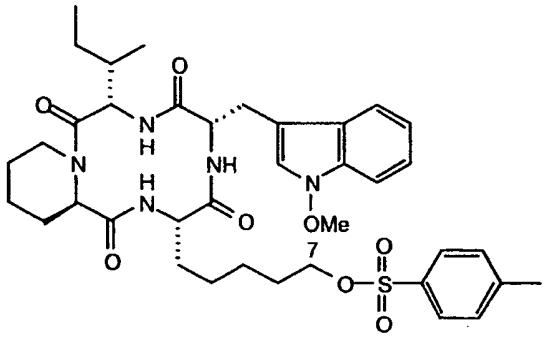
Method A

Following the general procedure of Example 7, the C6-aldehyde of Example 58a was converted into Example 42 by adding 2.1mg $NaBH_4$ to 64mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-6-oxo-hexanoyl) in 1mL 1:1 THF:EtOH at 0°C. After 1h, the resulting solution was poured into saturated NH_4Cl, extracted exhaustively with CH_2Cl_2 and 3:7 *i*PrOH:$CHCl_3$ (1x). The organic layer was dried with Na_2SO_4. Pure Example 42 was obtained following PTLC on silica gel (1 x 500μm plate) using 1:1 acetone:hexanes as eluant. Example 42 was characterized by ^1H NMR and MS [m/z: 570 (M^++1)].

Method B

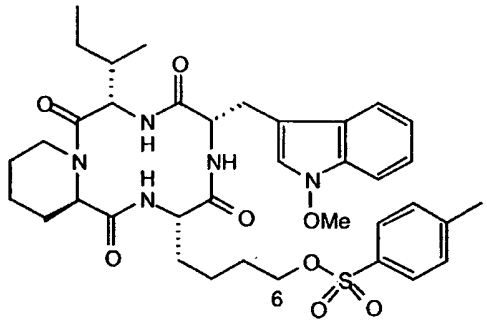
7.3mg of a ~1:1 mixture of 6,7- and 9,10-enones of apicidin, Example 55a and 55b, was placed in 1mL CH_2Cl_2 at -78°C. Ozone was bubbled through the solution until a blue color persisted. A vigorous stream of nitrogen was then used to remove the excess ozone. To this solution was added 3.6mg $NaBH_4$ in 120μL 1:1 EtOH:H_2O, the cooling bath was removed and the solution was aged overnight. The solution was poured into saturated NH_4Cl(aq), extracted with CH_2Cl_2 and dried with Na_2SO_4. Pure Example 42 was obtained following PTLC purification on silica gel (1 x 500μm plate) using 1:1 acetone:hexanes as eluant.

EXAMPLE 43



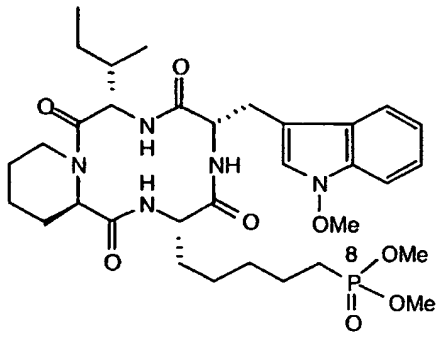
Example 43 was prepared by the following procedure. To 32mg Example 41, *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-hydroxy-heptanoyl), in 2.5mL CH_2Cl_2 at 0°C, was added 27μL DIEA, a catalytic amount of DMAP, and 36mg toluene sulfonic anhydride. After 1h at 0°C and 12h at RT, the solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following preparative TLC on silica gel (2 x 1000μm plates) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant. 20mg pure Example 43 product was obtained and was characterized by ^1H NMR and MS [m/z: 755.5 (M^++NH_4)]. TLC: R_f = 0.58 (1:3:96 NH_4OH:MeOH:$CHCl_3$).

EXAMPLE 44



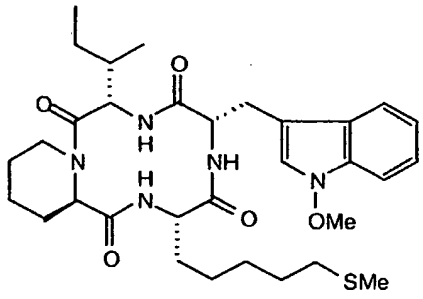
Example 44 was prepared from Example 42 *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-6-hydroxy-hexanoyl) by following the general procedure of Example 43, and was characterized by ^1H NMR and MS [m/z: ??? (M^++NH_4)].

EXAMPLE 45



Example 45 was prepared by the following procedure. To 9μL $(MeO)_2P(O)H$ in 350μL THF was added 2.5mg 95% NaH at RT via syringe and the solution heated to reflux for 20min. The solution was then cooled to RT and 25mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-(*para*-toluenesulfonyl)-heptanoyl) was added as a solution in 350μL THF, heated to reflux for 2h, cooled to RT and stirred for 12h. The solution was poured into saturated $NaHCO_3$, extracted CH_2Cl_2 and dried with Na_2SO_4. Pure 4.1mg Example 45 product was obtained following PTLC (1 x 1000μm plate) on silica gel using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant. The pure product was characterized by ^1H NMR and MS [m/z: 676 (M^++1)].

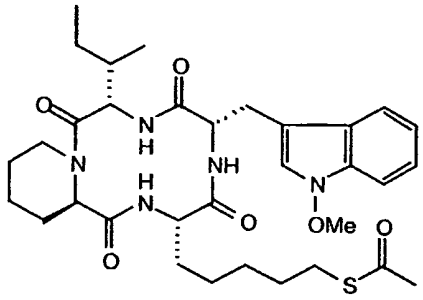
EXAMPLE 46



Example 46 was prepared by the following procedure. To 5mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-(*para*-toluenesulfonyl)-heptanoyl) in 1mL DMF at RT was added 5mg NaSMe. After 2h, the solution was poured into brine, extracted with CH_2Cl_2 and dried with Na_2SO_4. The pure Example 46 product was obtained following preparative TLC on silica gel (1 x 500μm plate) using 1:2

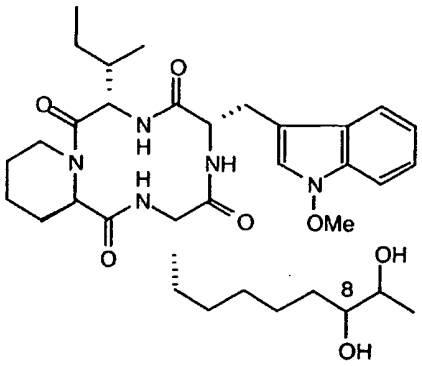
acetone:hexanes as eluant. The pure product was characterized by ^{1}H NMR and MS [m/z: 614.5 (M^++1)]. TLC: R_f = 0.33 (1:2 acetone:hexanes).

EXAMPLE 47



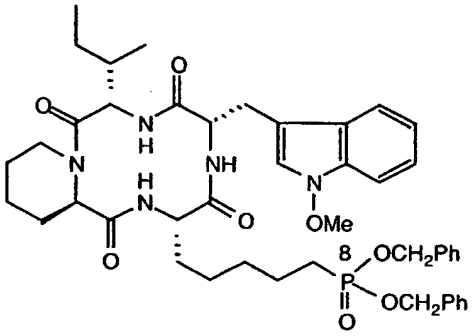
Example 47 was prepared by the following procedure. To 5mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-(*para*-toluenesulfonyl)-heptanoyl) in 1mL DMF at RT was added 5mg NaSAc. After 2h, the solution was poured into brine, extracted with CH_2Cl_2 and dried with Na_2SO_4. Pure Example 47 product was obtained following preparative TLC on silica gel (1 x 500μm plate) using 1:2 acetone:hexanes as eluant. The pure product was characterized by ^{1}H NMR and MS [m/z: 642.5 (M^++1)]. TLC: R_f = 0.22 (1:2 acetone:hexanes).

EXAMPLE 48



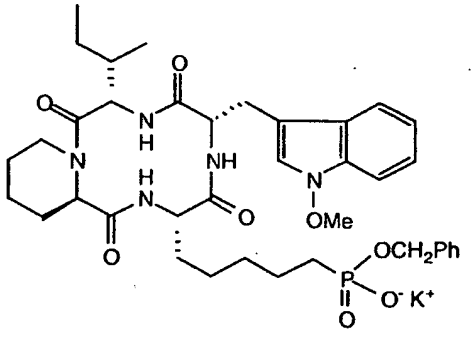
Example 48 was prepared by starting with Example 22b and following the general procedure described for Example 7. Example 22b's C8 ketone group was converted to a hydroxyl to form Example 48, which was characterized by ^{1}H NMR.

EXAMPLE 49



Example 49 was prepared by the following procedure. A solution of 63μL dibenzyl phosphonate in 1mL THF was added via syringe to 7mg 95% NaH and the solution heated to reflux for 20min. The mixture was cooled to RT and 70mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-(*para*-toluenesulfonyl)-octanoyl) was added as a solution in 1mL THF. The resultant white, heterogeneous solution was heated to reflux for 2h followed by 12h at RT. The solution was added to water, extracted with CH_2Cl_2 and dried with Na_2SO_4. Pure 26mg Example 49 was obtained following PTLC on silica gel (1 x 1500μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant. The product was characterized by ^1H NMR and MS [m/z: 828 (M^++1)].

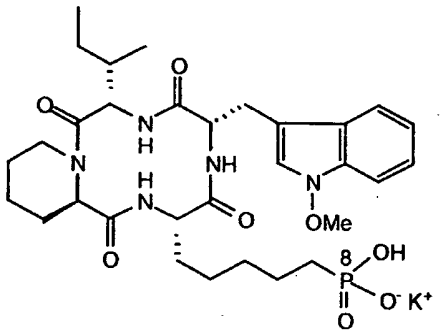
EXAMPLE 50



Example 50 was prepared by the following procedure. To 11mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-dibenzylphosphono-octanoyl), in 2mL *i*PrOH containing 44μL H_2O and 1.3mg $KHCO_3$ at RT was added 1mg 10%

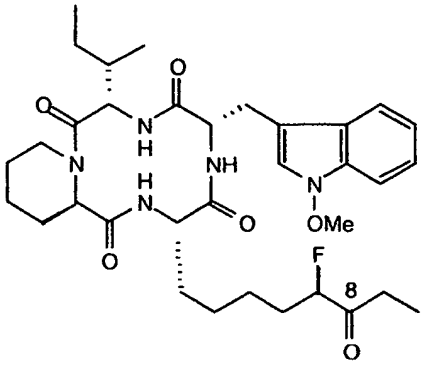
Pd/C. An atmosphere of H_2 was established (balloon pressure). After 12h, the catalyst was removed by filtration through Celite using 1:1 MeOH:H_2O as eluant. The solution was concentrated *in vacuo* and the residue was washed with $CHCl_3$ followed by EtOAc. The remaining glassy material was lyophilized from water to yield 3mg product. The product was characterized by ^1H NMR and MS [m/z: 738 (M^++1)].

EXAMPLE 51

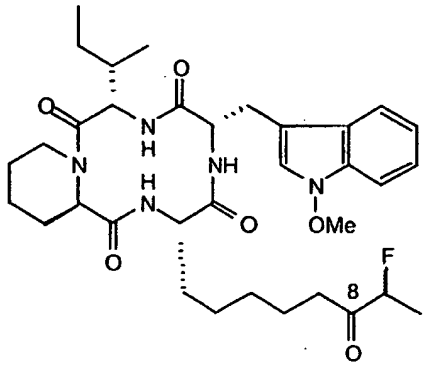


Example 51 was prepared by the following procedure. To 2mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-dibenzylphosphono-octanoyl) in 0.35mL *i*PrOH was added 8μL water, 0.25mg $KHCO_3$ and 0.5mg 10% Pd/C and a balloon atmosphere of hydrogen was established. After 7h at RT, the catalyst was removed via filtration through Celite and washed with water. 3mg of pure Example 51 product was characterized by ^1H NMR and MS [m/z: 648 (M^++1)].

EXAMPLES 52A AND 52B



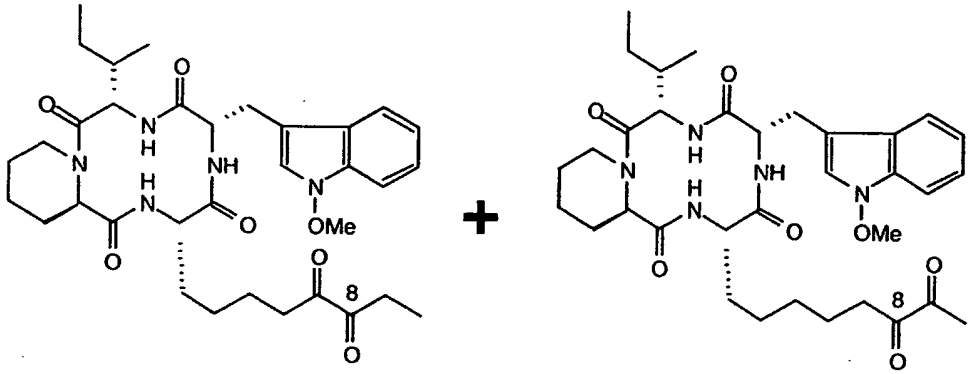
Ex. 52a



Ex. 52b

Examples 52a and 52b were prepared by the following procedure. To 3mg ~1:1 *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-hydroxy-8-oxo-decanoyl) and *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-9- hydroxy -8-oxo-decanoyl) 3mg) in 0.25mL CH_2Cl_2 at -78°C was added powdered, activated 4Å sieves followed by 1.5μL Et_2NSF_3. The solution was warmed to -10°C over 1h and then quenched by the addition of saturated $NaHCO_3$. The solution was extracted with CH_2Cl_2 and dried with Na_2SO_4. A pure mixture of approximately 1:1 Example 52a and 52b was obtained following PTLC on silica gel (1 x 500μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant. 2.5mg of the mixture were characterized by ^1H NMR and MS [m/z: 641 (M^++1)].

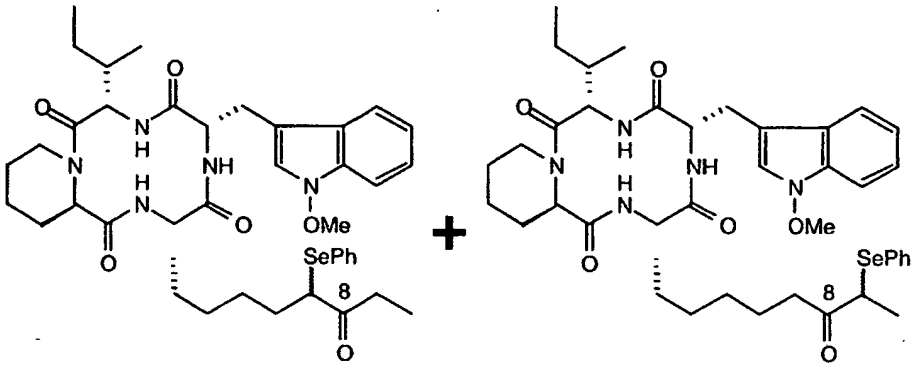
EXAMPLES 53A AND 53B



Ex. 53a **Ex. 53b**

Examples 53a and 53b were prepared by the following procedure. To 6mg ~1:1 *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-hydroxy-8-oxo-decanoyl) and *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-9-hydroxy-8-oxo-decanoyl), Examples 20a and 20b, at RT was added powdered, activated 4Å sieves followed by 3mg N-methylmorpholine-N-oxide and 0.3mg TPAP. After 1h, the mixture was diluted with CH_2Cl_2 and filtered through Celite using CH_2Cl_2 as eluant. The filtrate was extracted with 10% $NaHSO_3$(aq), washed with water, and dried with Na_2SO_4. Pure products were obtained following PTLC (1 x 500 μm plate) separation using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant. 3.5mg of each pure Example 53a and 53b were characterized by ^1H NMR and MS [m/z: 637 (M^++1)].

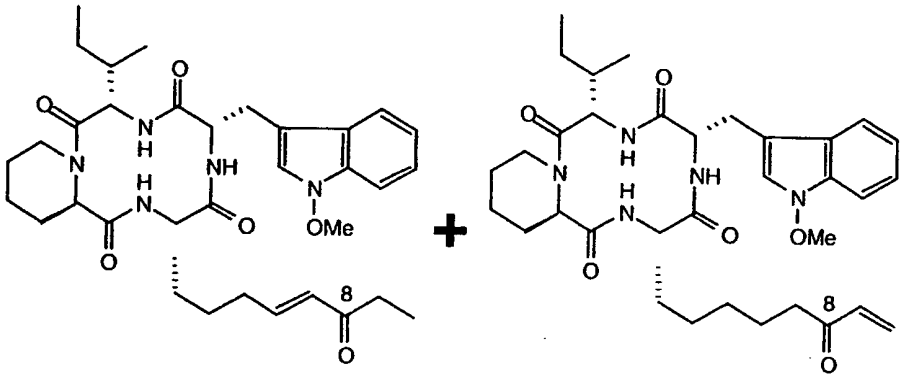
EXAMPLES 54A AND 54B



Ex. 54a **Ex. 54b**

Examples 54a and 54b were prepared by the following procedure. To 2g apicidin in 32mL THF at 0°C was added 14mL 0.5M potassium hexamethyldisilazane solution in toluene. The solution was aged at 0°C for 30min. Next, 25.g solid PhSeCl was added and the solution was warmed to RT for 2h. The reaction was quenched by the addition of saturated $NaHCO_3$(aq), was extracted with CH_2Cl_2, dried with Na_2SO_4 and filtered through 8 x 14 cm plug of silica gel using gradient elution (hexanes to 1:1 EtOAc:hexanes to 1:1 acetone:hexanes). The product was used in the preparation of Examples 55a and 55b with no further purification. The 2.3g mixture thus obtained was characterized by ^1H NMR and MS [m/z: 780.3 (M^++1)]. TLC: R_f = 0.60 (1:3:96 NH_4OH:MeOH:$CHCl_3$).

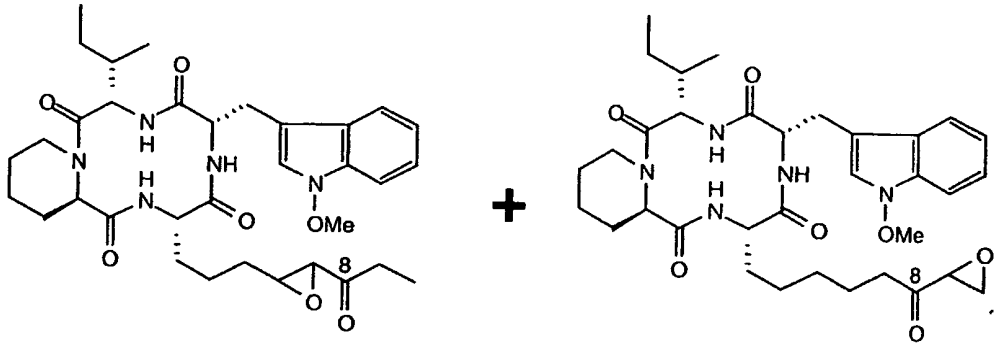
EXAMPLES 55A AND 55B



Ex. 55a **Ex. 55b**

Examples 55a and 55b were prepared by the following procedure. To 2.2g ~1:1 *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-7-phenylselenyl-decanoyl) and *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-9-phenylselenyl-decanoyl) in 40mL THF at 0°C was added 7.3mL 30% H_2O_2. The solution was warmed to 50°C and after 10min was cooled to 0°C, quenched with saturated $Na_2S_2O_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4 Following purification on silica gel using 4:6 acetone:hexanes as eluant, a 230mg pure mixture of Examples 55a and 55b was characterized by ^1H NMR and MS [m/z: 622.3 (M^++1)]. TLC:. R_f = 0.38 (1:3:96 NH_4OH:MeOH:$CHCl_3$).

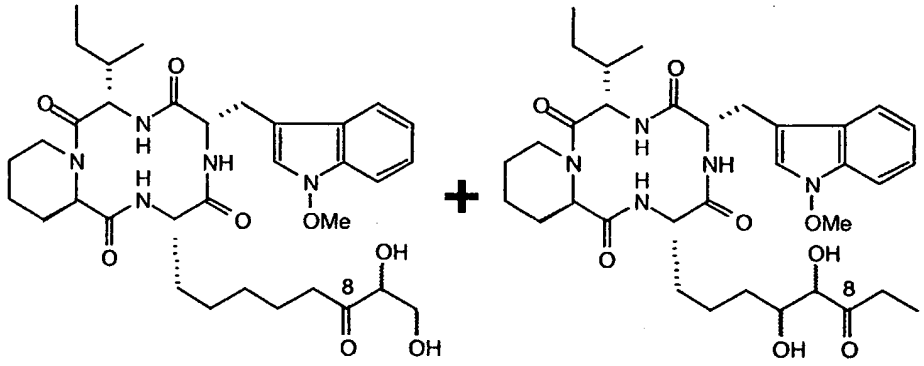
EXAMPLES 56A AND 56B



Ex. 56a **Ex. 56b**

Examples 56a and 56b were prepared by the following procedure. To 5.6mg ~1:1 *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-6,7-dehydro-decanoyl) and *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-9,10-dehydro-decanoyl) in 0.225mL THF at RT was added 0.8mL $PhCH_2N(Me)_3$ (40% solution in MeOH) followed by 1.5mL 70% *t*-BuOOH(aq). After 4.5h, EtOAc and minimal water were added and the aqueous phase thoroughly extracted with EtOAc. The organic layer was washed with cold 1N HCl (1x), quickly washed again with saturated $NaHCO_3$, and then dried with Na_2SO_4. Pure products were separated by PTLC (1 x 500μm plate) using 4:6 acetone:hexanes as eluant. The pure examples 56a and 56b were characterized by ^{1}H NMR. The procedure yielded 1.4mg *cyclo*(N-O-Methyl-L-Trp-L-Ile-D-Pip-L-2-amino-6,7-oxiranyl-decanoyl); MS [m/z: 638 (M+1)]; TLC: R_f = 0.4 (4:6 acetone:hexanes). The procedure yielded 2mg *cyclo*(N-O-Methyl-L-Trp-L-Ile-D-Pip-L-2-amino-9,10-oxiranyl-decanoyl); MS [m/z: 638 (M+1)]; TLC: R_f = 0.3 (4:6 acetone:hexanes).

EXAMPLES 57A AND 57B

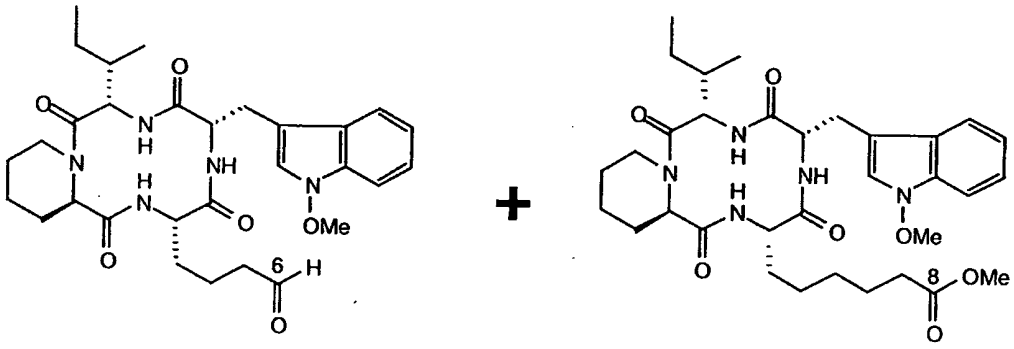


Ex. 57a **Ex. 57b**

Example 57a and 57b were prepared by the following procedure. To 115mg ~1:1 *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-6,7-dehydro-decanoyl) and *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-9,10-dehydro-decanoyl) in 4mL 8:1 acetone:water at 0°C was added 45mg trimethylamine-N-oxide followed by 0.77mL 0.024M OsO_4(aq). The solution was warmed to RT for 3h and then aged at 4°C for 12h. The brown homogenous solution was quenched at 0°C by the addition of 2mL 10% $NaHSO_3$(aq). After 10min, brine was added and the

solution thoroughly extracted with 3:7 *i*PrOH:$CHCl_3$ (9x) and dried with Na_2SO_4. The solvent was removed *in vacuo* to yield 230mg crude product (121mg theoretical) which was used with no additional purification. A small aliquot of the regioisomeric diols were separated by PTLC on silica gel (1 x 1000μm plate) using 1:1 acetone:hexanes as eluant and the products were characterized by ^1H NMR and MS. *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-6,7-dihydroxy-decanoyl): MS [m/z: 656 (M^++1)]; TLC: R_f = 0.5 (4:6 acetone:hexanes). *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-9,10-dihydroxy-decanoyl): MS [m/z: 656 (M^++1)]; TLC: R_f = 0.25 (4:6 acetone:hexanes).

EXAMPLES 58A AND 58B



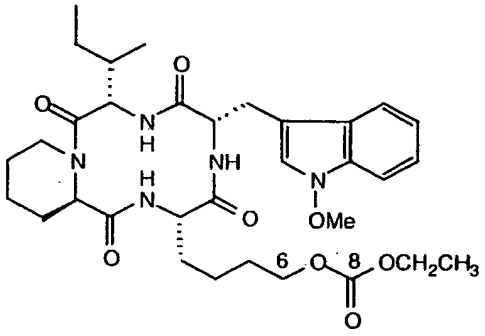
Ex. 58a **Ex. 58b**

Examples 58a and 58b were prepared by the following procedure. To 121mg ~1:1 *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-6,7-dihydroxy-decanoyl) and *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-9,10-dihydroxy-decanoyl) in 6mL MeOH at 0°C was added 75mL pyridine followed by 184mg $Pb(OAc)_4$. After 40min, the solution was poured into saturated $Na_2S_2O_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Pure separated Examples 58a and 58b were obtained following PTLC (3 x 1500μm plate) on silica gel using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant. The pure products were characterized by ^1H NMR and MS.

Example 58a, *cyclo*(N-O-Methyl-L-Trp-L-Ile-D-Pip-L-2-amino-6-oxo-hexanoyl): Yield: 30mg. MS [m/z: 568 (M^++1)]; TLC: R_f = 0.45 (1:1 acetone:hexanes).

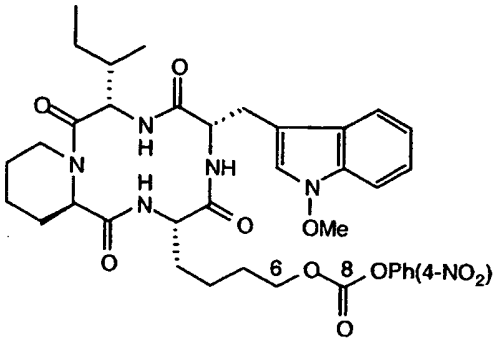
Example 58b, *cyclo*(N-O-Methyl-L-Trp-L-Ile-D-Pip-L-2-amino-7-carboxymethyl-heptanoyl): Yield: 20mg.

EXAMPLE 59



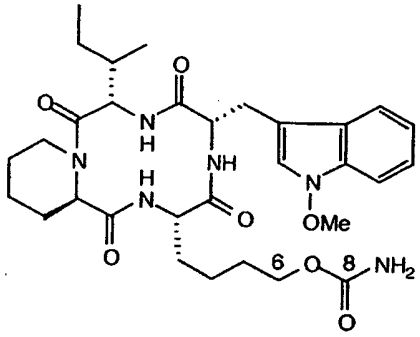
Example 59 was prepared by the following procedure. To 4mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-6-hydroxy-hexanoyl) in 0.14mg CH_2Cl_2 and 1mL pyridine at 0°C was added 1mL ethyl chloroformate. The solution was warmed to RT, aged for 3h and the solvents removed *in vacuo*. 1.3mg pure Example 59 was obtained following PTLC (1 x 500μm plate) on silica gel using 4:6 acetone:hexanes as eluant. The pure product was characterized by ^{1}H NMR and MS [m/z: 659 (M^++NH_4)].

EXAMPLE 60



Example 60 was prepared by the following procedure. 7.5mg of the Example 64 C6-alcohol was placed in about 1mL CH_2Cl_2 at 0°C to which was added 3.2mg (4-NO_2)PhOC(O)Cl followed by 1.3µL pyridine. After 2h at 0°C, the volatiles were removed under reduced pressure without workup and 9mg pure Example 60 product was obtained following PTLC on silica gel (1 x 500µm plate) using 1:1 acetone:hexanes as eluant. The pure Example 60 thus prepared was characterized by ^{1}H NMR and MS [m/z: 735 (M^++1)].

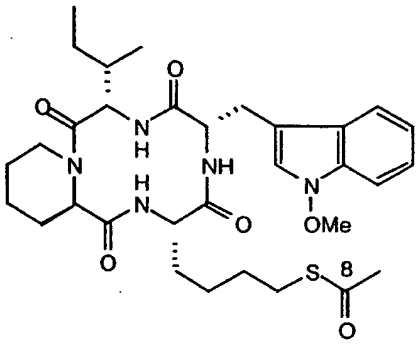
EXAMPLE 61



Example 61 was prepared by the following procedure. Anhydrous ammonia was bubbled into 2mL dioxane at 0°C to generate a ~0.5 M solution. This solution was added to 6mg solid *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-6-*para*-nitrophenoxycarbonyloxy-hexanoyl) at 0°C. The ice bath was removed and the solution aged at RT for 2h. The solution was concentrated under reduced pressure and 1.7mg pure Example 61 was obtained following PTLC (1 x 500µm plate) using 1:9:90

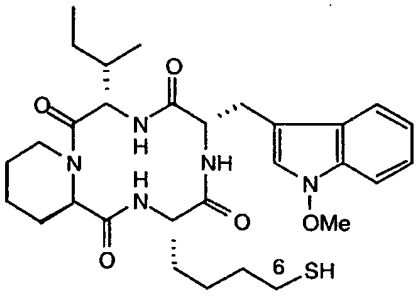
NH_4OH:MeOH:$CHCl_3$ as eluant, and was characterized by ^1H NMR and MS [m/z: 613 (M^++1)].

EXAMPLE 62



Example 62 was prepared by the following procedure. To 4mg Ph_3P in 0.2mL THF at 0°C was added 2.4mL DEAD (diethyl azodicarboxylate) and aged for 30min. To this resulting solution was added about 4mg solid *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-6-hydroxy-hexanoyl) at 0°C. After 1h at 0°C, the solution was warmed to RT for 1h. Solvent was removed under reduced pressure. 2mg of pure Example 62 product was obtained following PTLC (1 x 250μm plate) using 1:1 acetone:hexanes as eluant and was characterized by ^1H NMR and MS [m/z: 628 (M^++1)].

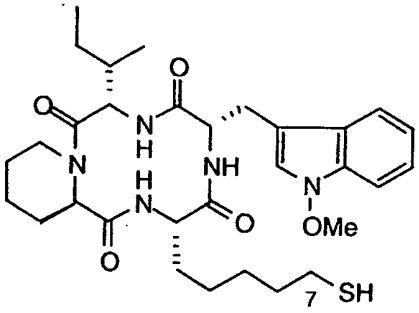
EXAMPLE 63



Example 63 was prepared by the following procedure. To 1.5mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-6-acetylthio-hexanoyl) in 0.2mL MeOH at 0°C was added 0.3mL 25 wt % NaOMe in MeOH. After 5h, water was

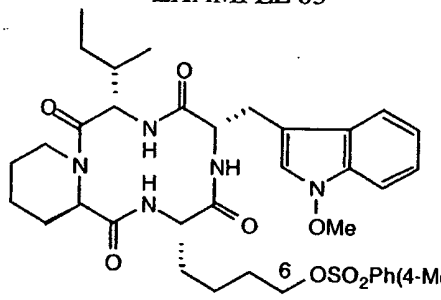
added to quench the reaction. The solution was extracted with CH_2Cl_2 and dried with Na_2SO_4. 0.5mg pure Example 63 product was obtained following PTLC (1 x 250μm plate) using 1:1 acetone:hexanes as eluant. Example 63 was characterized by ^1H NMR and MS [m/z: 588 (M^++1)].

EXAMPLE 64



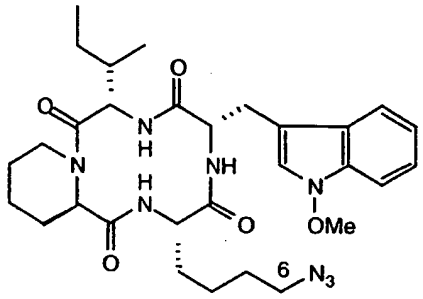
Following the general procedure of Example 63, the C7 thiol was prepared from the corresponding thioacetate of Example 47. Example 64 was characterized by ^1H NMR and MS [m/z: 599 (M^++1)].

EXAMPLE 65



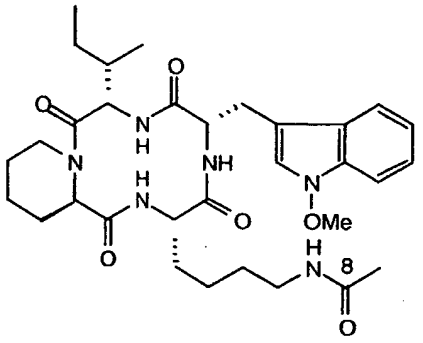
Example 65 was prepared by the following procedure. To 1.6mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-6-hydroxy-hexanoyl) in 0.28mL CH_2Cl_2 at 0°C was added 0.2mg DMAP followed by 2mg TsCl. After 16h, the solution was aged at RT for 16h. The solvent was removed under reduced pressure. Following PTLC (1 x 250μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, 0.3mg pure Example 65 was obtained. The pure product was characterized by ^1H NMR and MS [m/z: 724 (M^++1)].

EXAMPLE 66



Example 66 was prepared by the following procedure. To 4mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-6-hydroxy-hexanoyl) in 0.35mL CH_2Cl_2 at 0°C was added i) 3.7mg PPh_3, ii) 1mg imidazole and iii) 3.2mg $Zn(N_3)_2$•(pyridine)$_2$ followed by iv) 2.2μL DEAD. The solution was warmed to RT for 12h. Following PTLC (1 x 500μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, 2mg pure Example 66 was obtained. Example 66 was characterized by ^1H NMR and MS [m/z: 595 (M^++1)].

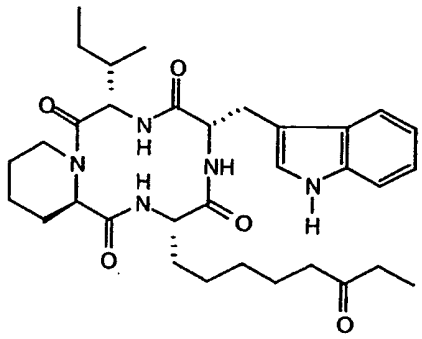
EXAMPLE 67



Example 67 was prepared by the following procedure. To 1mg *cyclo*(N-O-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-6-azido-hexanoyl) at 0°C in 0.1mL THF was added 0.1mL thiolacetic acid. After 1h, the solution was warmed to RT for 1h. The solvents were then removed with a vigorous stream of nitrogen. The residue was dissolved in 0.2mL neat thiolacetic acid, aged for 4h and then concentrated with a vigorous stream of nitrogen. Pure Example 67 product was obtained following PTLC

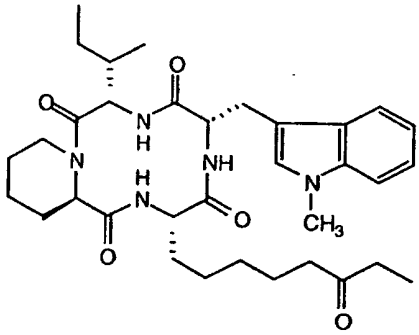
(1 x 250μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant. The pure product (0.7mg) was characterized by ^1H NMR and MS [m/z: 611 (M^++1)].

EXAMPLE 68



Example 68 was prepared by the following procedure. 40mg $Pd(OH)_2$ was added to 500mg apicidin in 40mL 1:1 THF:MeOH. An H_2 atmosphere was established (balloon pressure). After 12h, the palladium catalyst was removed by filtration through Celite using MeOH as eluant. Following flash chromatography on silica gel using 4:6 acetone:hexanes as eluant, 467mg pure Example 68 product was obtained and was characterized by ^1H NMR. TLC: R_f = 0.18 (1:2 acetone:hexanes). HPLC: t_R = 7.54min (1:1 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

EXAMPLE 69



Example 69 was prepared by the following methods:

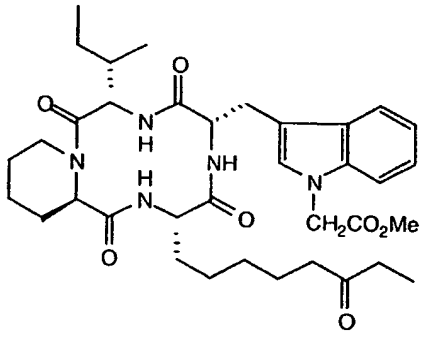
Method C

To 30mg N-desmethoxy apicidin in 500μL DMF at RT was added 4 drops MeI followed by the addition of 11mg *t*BuOK. The solution was stirred for 2h at RT, 12h at 4°C and then for another 4h at RT. The solution was then heated at 60°C for 1.5h and cooled back to RT. An additional 20mg *t*BuOK was added and the solution stirred for 1h. The solution was then poured into 3mL of 1:2 saturated $NaHCO_3$:saturated brine, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following preparative TLC on silica gel (2 x 1500μm plates) using 1:2 acetone:hexanes as eluant, 19mg pure Example 69 was obtained and was characterized by ^1H NMR and MS [m/z: 625.3 (M^++NH_4)]. TLC: R_f = 0.31 (1:2 acetone:hexanes). HPLC: t_R = 3.90min (62:38 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

Method D

1.3mg 60% NaH was added to 20mg N-desmethoxy apicidin in 0.35mL DMF at RT). After 30min, 4μL MeI was added and the solution stirred for 10h. The solution was then poured into saturated NH_4Cl, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following preparative TLC on silica gel (1 x 500 μm plate) using 1:1 acetone:hexanes as eluant, and further purification by preparative RP-HPLC using a linear gradient (1:1 to 1:0 MeCN:H_2O), 5mg pure Example 69 was obtained which was characterized by ^1H NMR and MS [m/z: 608.5 (M^++1)].

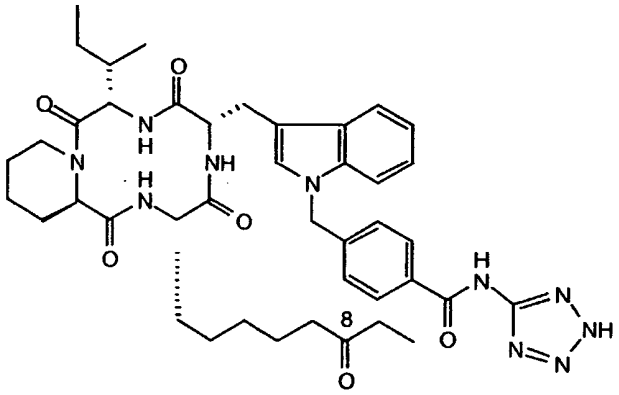
EXAMPLE 70



Example 70 was prepared by the following procedure. At RT, 467mg N-Desmethoxy apicidin was placed in 16mL DMF to which was added 63mg 60% NaH. After 10min, 206μL $BrCH_2CO_2Me$ and 871mg *n*Bu4NI were added and the

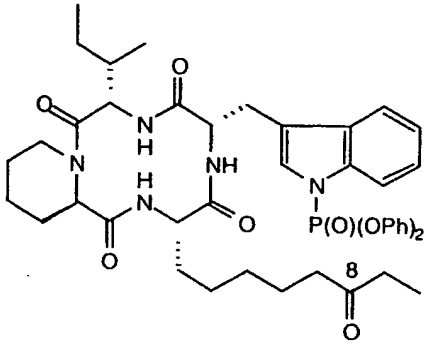
solution heated to 80°C. After 15min, the solution was poured into water, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following flash chromatography on silica gel using 1:1 acetone:hexanes as eluant, 401mg pure Example 70 was obtained which was characterized by ^1H NMR and MS [m/z: 666 (M^++1)]. TLC: R_f = 0.46 (1:1 acetone:hexanes). HPLC: t_R = 7.21min 1:1 MeCN:H_2O, 1.0mL/min, Zorbax™ RX-8).

EXAMPLE 71



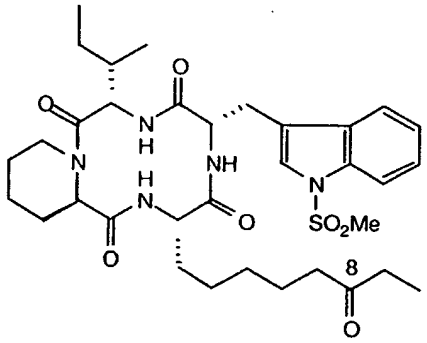
Example 71 was prepared by the following procedure. At 0 °C, 0.65mg HOBT, 1.6mg $NaHCO_3$, 0.5mg 5-aminotetrazole and 1mg EDCI was added to 3.5mg N-desmethoxy-N-(para-carboxyphenylmethyl) apicidin in DMF. After 12h, the solution was poured into saturated $NHCl_4$, extracted with CH_2Cl_2 and dried with Na_2SO_4 Following RP-HPLC using gradient elution (4:6 to 1:0 MeCN:water), 1.6mg pure Example 71 was obtained which was characterized by ^1H NMR and MS [m/z: 795 (M^++1)].

EXAMPLE 72



Example 72 was prepared by the following procedure. At RT, 3.4mg 60% NaH was added to 50mg N-desmethoxy apicidin in 0.2mL DMF and 0.2mL HMPA. After gas evolution ceased, 35μL $(PhO)_2P(O)Cl$ was added. After 24h, the solution was poured into water, extracted with EtOAc and dried with Na_2SO_4. Following preparative chromatotron TLC (1000μm plate) using 1:2 acetone:hexanes as eluant, 16mg pure Example 72 was obtained which was characterized by ^1H NMR and MS [m/z: 826 (M^++1)].

EXAMPLE 73



Example 73 was prepared by the following procedure. At RT, 7mL Et_3N, and 1mg DMAP was added to 10mg N-desmethoxy apicidin in 0.17mL CH_2Cl_2. Then 3.9μL $MeSO_2Cl$ was added. After 20h, the solution was poured into water, extracted with EtOAc and dried with Na_2SO_4. Following preparative RP-HPLC using a linear gradient (4:6 to 1:0 MeCN:H_2O), 0.6mg pure Example 73 was

obtained (R_f = 0.4, 4:6 acetone:hexanes) which was characterized by ^{1}H NMR and MS [m/z: 672 (M^++1)].

EXAMPLES 74A-74J

Following the general procedure of Examples 69-72, utilizing an appropriate electrophile (R-X) readily determined by one in the art, the following compounds were prepared:

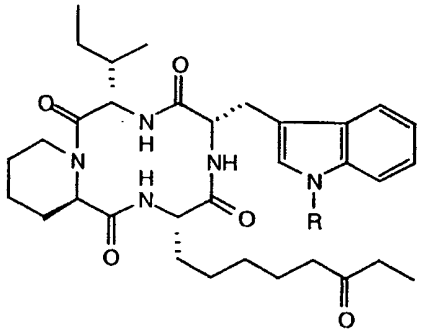
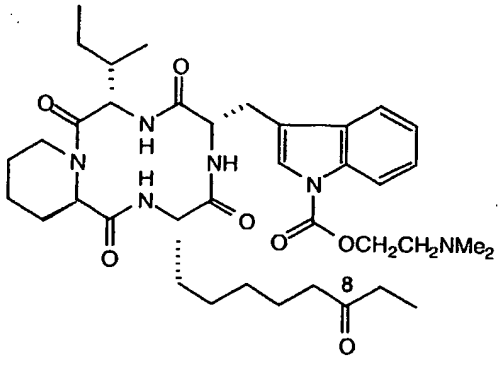


Table 6

Example	R Group	Mass Spec
69	Me	608.5 (M^++1)
70	CH_2CO_2Me	666 (M^++1)
71	CH_2Ph[4-C(O)NH(5-tetrazolyl)]	795 (M^++1)
72	$P(O)(OPh)_2$	826 (M^++1)
73	SO_2Me	672 (M^++1)
74a	Et	639.4 (M^++NH_4)
74b	*n*Pr	653.3 (M^++NH_4)
74c	CH_2CO_2tBu	708 (M^++1)
74d	$CH_2CH_2OSi(t$Bu)Me_2	752 (M^++1)
74e	$CH_2Ph(4\text{-}CO_2Me)$	742 (M^++1)
74f	C(O)Ph(4-Oac)	756 (M^++1)
74g	C(O)Ph	698 (M^++1)
74h	$CO_2Ph(4\text{-}NO_2)$	759 (M^++1)
74i	CO_2CH_2Ph	728 (M^++1)
74j	SO_2Ph(4-Me)	748 (M^++1)
75	$CO_2CH_2CH_2NMe_2$	709 (M^++1)

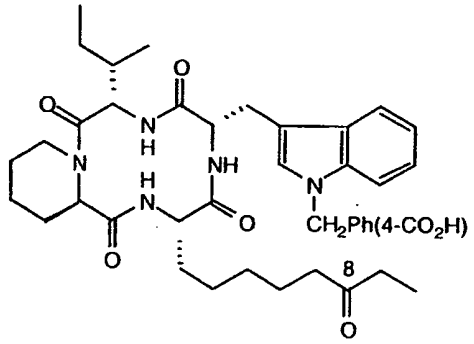
EXAMPLE 75



Example 75 was prepared by the following procedure. At RT, 0.1mL pyridine was added to 9mg N-desmethoxy-N-(*para*-aminophenoxycarbonyl) apicidin in 0.22mL DMF, followed by the addition of 22μL $HOCH_2CH_2NMe_2$. After 15h,

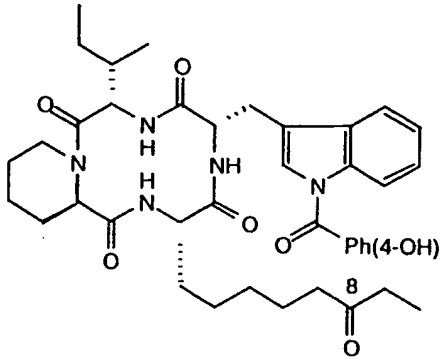
the solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following preparative chromatotron TLC (1000μm plate) using 1:2 acetone:hexanes as eluant, pure Example 75 was obtained which was characterized by ^1H NMR and MS [m/z: 709 (M^++1)].

EXAMPLE 76



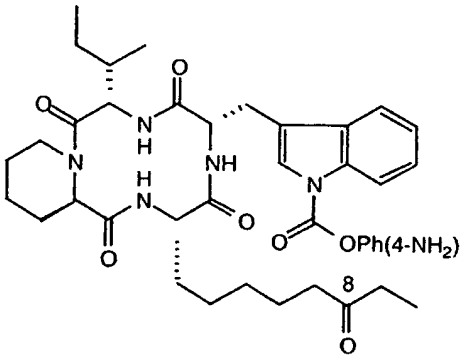
Example 76 was prepared by the following procedure. At 0°C, 7.8μL 1N LiOH was added to 3.8mg N-desmethoxy-N-(*para*-carboxymethylphenylmethyl) apicidin in 0.13mL of a 3:1:1 mixture of THF:MeOH:H_2O. After 2h at 0°C and 17h at RT, the volatiles were then removed with a vigorous stream of nitrogen. The aqueous layer was then extracted with EtOAc and the aqueous layer acidified to pH~4 with 2N HCl. The aqueous layer was further extracted with 5 aliquots of a 3:7 mixture of *i*PrOH:$CHCl_3$ and finally dried with Na_2SO_4. Following RP-HPLC using a linear gradient (2:8 to 1:0 MeCN:H_2O), 2.5mg pure Example 76 was obtained which was characterized by ^1H NMR and MS [m/z: 728 (M^++1)].

EXAMPLE 77



Example 77 was prepared by the following procedure. At -10°C, 6.5μL 1M LiOH was added to a solution of 3.3mg N-desmethoxy-N-(*para*-acetoxyphenylcarbonyl) apicidin in 0.11mL of a 3:1:1 mixture of THF:MeOH:H_2O. After 1h, the volatiles were removed with nitrogen. Then, about 2mL each of water and EtOAc was added. The resulting solution was carefully neutralized to pH~7 with 2N HCl. The solution was extracted with EtOAc and dried with Na_2SO_4. Following PTLC (1 x 500μm plate) using 6:4 acetone:hexanes as eluant, 1.7mg pure Example 77 was obtained which was characterized by ^1H NMR and MS [m/z: 714 (M^++1)].

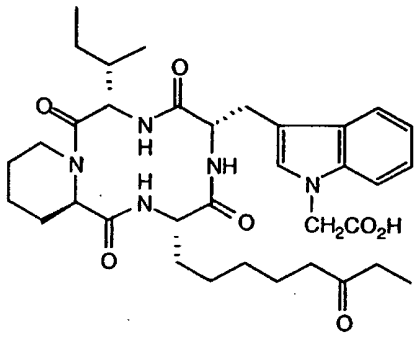
EXAMPLE 78



Example 78 was prepared by the following procedure. At RT, 0.5mg 10% Pd/C catalyst was added to 2mg N-desmethoxy-N-(*para*-nitrophenoxycarbonyl)-apicidin in 0.2mL CH_2Cl_2 and an atmosphere of hydrogen established (balloon pressure). After 6.5h, the catalyst was removed by filtration through Celite using 1:1

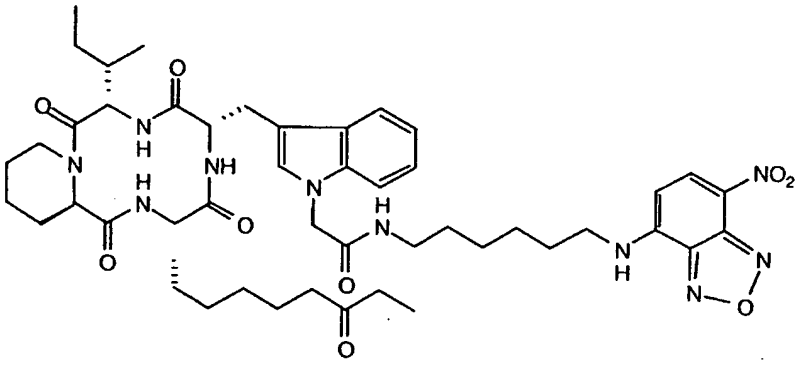
MeOH:CH_2Cl_2 as eluant. Without any further purification, the resulting 1.8mg Example 78 was characterized by ^1H NMR and MS [m/z: 729 (M^++1)].

EXAMPLE 79



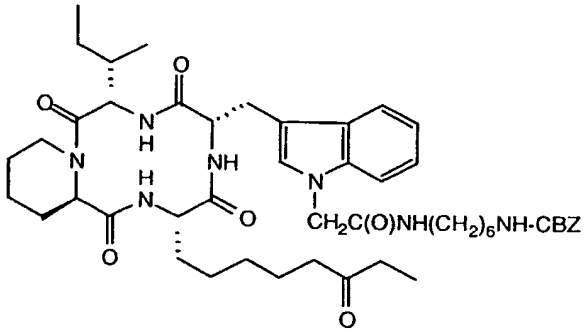
Example 79 was prepared by the following procedure. At 0°C, 200µL 1M LiOH was added to 89mg N-desmethoxy-N-carbomethoxymethyl apicidin in 3.5mL of a 1:1:1 mixture of THF:MeOH:H_2O. After 45min at 0°C, the slightly cloudy solution was warmed to RT and became homogenous. After an additional 20min, the MeOH and THF were removed using a vigorous stream of N_2. Then, 2mL Ethyl acetate was added to the solution and removed to dispose of residual organic soluble material. The solution was acidified to pH~4.0 using 2N HCl, 3mL brine was added to the aqueous layer, and then extracted with a 1:4 mixture of *i*PrOH:$CHCl_3$. The organic layer was dried with Na_2SO_4 to yield 51mg pure Example 79, which was characterized by ^1H NMR and MS [m/z: 652.5 (M^++1)]. HPLC: t_R = 1.21 min (1:1 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

EXAMPLE 80



Example 80 was prepared by the following procedure. At RT, 2.6mL TEA was added to 6mg N-desmethoxy-N-(6-amino-hexylaminocarbonylmethyl)-apicidin in 1mL CH_2Cl_2. Next, 4mg NBD-Cl was added and the vial was wrapped with foil. After 3h at RT, pure Example 80 was obtained by flash chromatography on silica gel without workup using 1:1 hexanes:acetone as eluant. The pure product was characterized by ^1H NMR. TLC: $R_f = 0.19$ (1:1 acetone:hexanes).

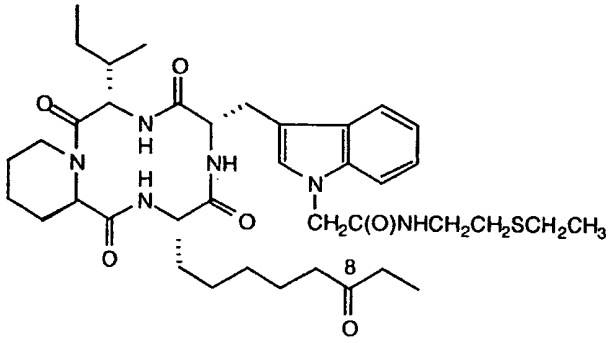
EXAMPLE 81



Example 81 was prepared by the following procedure. At 0 °C, 19mg EDCI was added to 50mg N-desmethoxy-N-carboxymethyl apicidin, 29mg CBZ-$HN(CH_2)_6NH_2$, 10mg HOBT and 19μL DIEA in 5mL CH_2Cl_2. After 15min at 0°C and 1h at RT, 3mg DMAP was added. After an additional 2 hours, the CH_2Cl_2 was removed using a vigorous stream of N_2 and 2mL DMF was added. After 2h, the solution was poured into 20μL 2:1 H_2O:brine, acidified to pH~3.0 with 2N HCl and

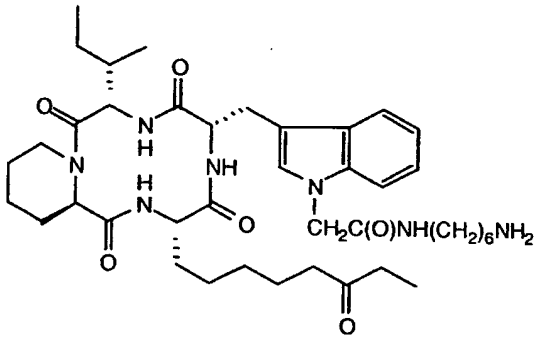
extracted with 5 15mL aliquots of CH_2Cl_2. The organic layer was dried with Na_2SO_4. Without further purification, 54mg pure Example 81 was obtained which was characterized by ^1H NMR and MS [m/z: 884.6 (M^++1)]. TLC: R_f = 0.72 (1:9:90 NH_4OH:MeOH:$CHCl_3$). HPLC: t_R = 5.38min (6:4 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

EXAMPLE 82



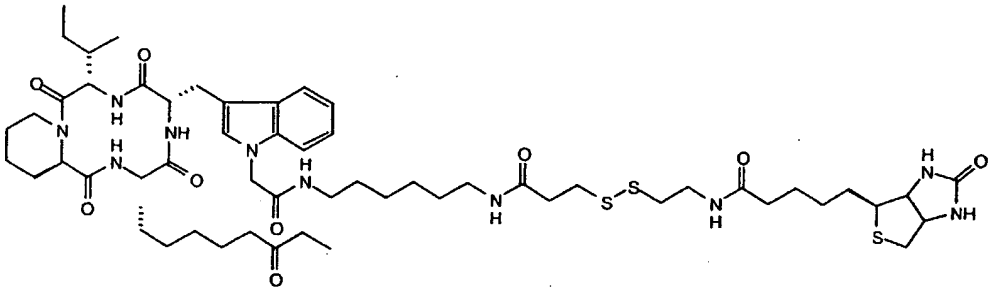
Example 82 was prepared by the following procedure. At 0°C, 1.2mg HOBT was added to 5.7mg N-desmethoxy-N-carboxymethyl apicidin in 0.1mL DMF, 2.9mg $NaHCO_3$, and 1.2mg $EtSCH_2CH_2NH_2$•HCl. This was followed by the addition of 1.8mg EDCI. The solution was warmed to RT and aged for 16h. The aged solution was poured into saturated $NaHCO_3$, extracted with EtOAc and dried with Na_2SO_4. Following RP-HPLC using gradient elution (4:6 to 1:0 MeCN:H_2O), 3.3mg pure Example 82 was obtained which was characterized by ^1H NMR and MS [m/z: 739 (M^++1)].

EXAMPLE 83



Example 83 was prepared by the following procedure. At RT, 10mg 5% Pd/C catalyst was added to 54mg N-desmethoxy-N-[6-(benzyloxycarbonylamino)-hexylaminocarbonylmethyl]-apicidin in 3mL DMF and a H_2 atmosphere (balloon pressure) was established. After 2h, an additional 40mg 5% Pd/C catalyst was added and the solution stirred overnight. The catalyst was then filtered off and the solvents were removed under reduced pressure. Following flash chromatography on silica gel using gradient elution (using first neat $CHCl_3$, then three subsequent elutions of 1:3:96, then 1:4:95 and then 1:9:90 NH_4OH:MeOH:$CHCl_3$ as eluant), pure Example 83 was obtained which was characterized by ^1H NMR and MS [m/z: 750.4 (M^++1)]. TLC: R_f = 0.12 (1:9:90 NH_4OH:MeOH:$CHCl_3$).

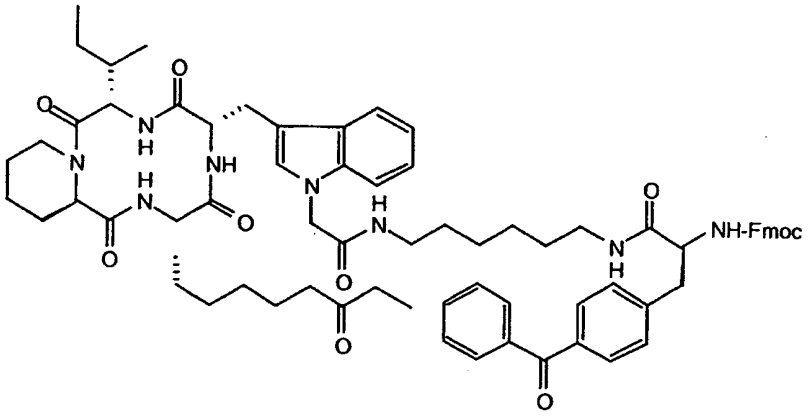
EXAMPLE 84



Example 84 was prepared by the following procedure. At RT, 3.2mg NHS-SS-Biotin was added to 4mg N-desmethoxy-N-(6-aminohexylaminocarbonylmethyl)-apicidin in 0.5mL CH_2Cl_2 followed by 2μL DIEA. The solution was stirred for 1h at RT, followed by 12h at 4°C and 2h at RT. Additional 3.2mg NHS-SS-Biotin and 2μL DIEA were added followed by 100μL

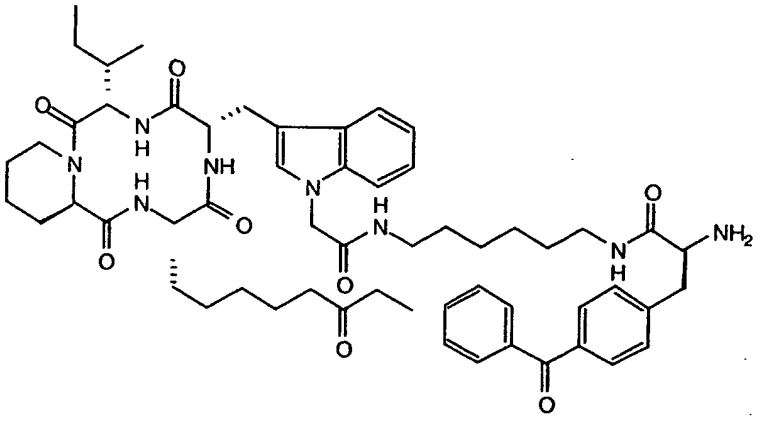
DMF. After an additional 1 hour, the solution was loaded directly onto a silica gel pipette column using gradient elution (1:3:96 to 1:9:90 NH_4OH:MeOH:$CHCl_3$ as eluant) to yield 4mg pure Example 84 which was characterized by ^1H NMR. TLC: R_f = 0.26 (1:9:90 NH_4OH:MeOH:$CHCl_3$).

EXAMPLE 85



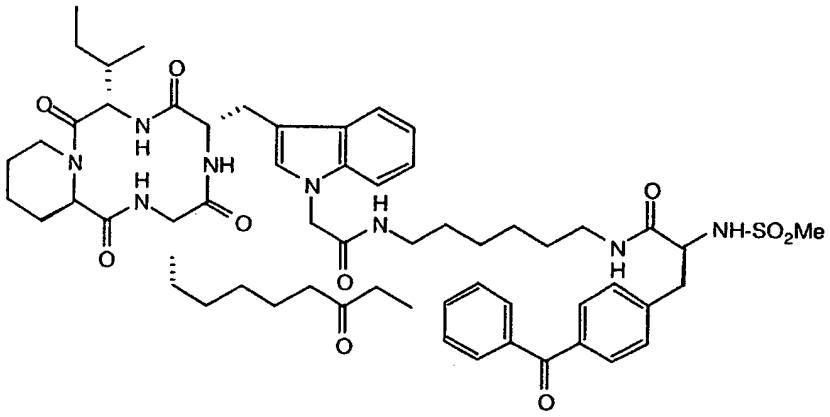
Example 85 was prepared by the following procedure. At RT, 0.5mg HOBT, 2.6mg Fmoc-Phe(4-Bz)-OH (Fmoc = 9-fluorenylmethyl oxycarbonyl) and 1mg EDCI was added to 2mg N-desmethoxy-N-(6-aminohexylaminocarbonylmethyl)-apicidin in 0.5mL CH_2Cl_2. Then, 3μL DIEA was added. After 2h at RT, the crude was purified without workup on a pipette flash column with silica gel using gradient elution (1:1 acetone:hexanes followed by 5:95 MeOH:$CHCl_3$). The partially purified Example 85 was characterized by ^1H NMR. TLC: R_f = 0.26 (1:9:90 NH_4OH:MeOH:$CHCl_3$). TLC: R_f = 0.53 (5:95 MeOH:$CHCl_3$).

EXAMPLE 86



Example 86 was prepared by the following procedure. At RT, 0.2mL piperidine was added to 15mg of the Fmoc-protected Example 85 compound in 2mL CH_2Cl_2. After 3h at RT, the volatiles were removed under reduced pressure to produce Example 86. This material was used with no additional purification in Example 87.

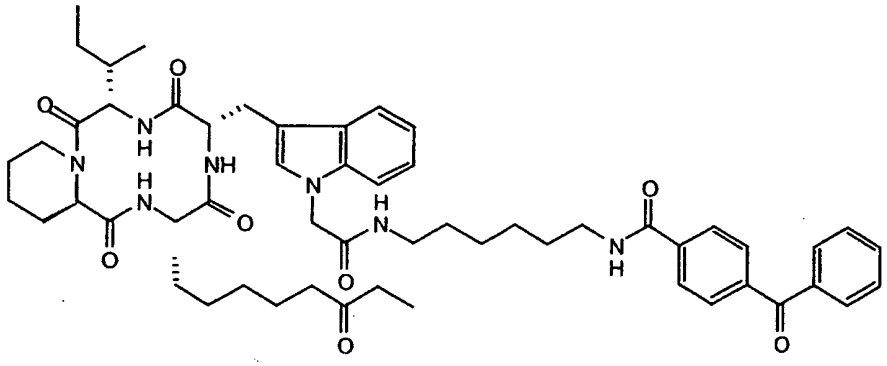
EXAMPLE 87



Example 87 was prepared by adding 5μL Et_3N to 2mg of the crude product of Example 86 in 0.2mL CH_2Cl_2 at 0 °C followed by 2μL $MeSO_2Cl$. After 30min, the reaction was quenched by the addition of 3 drops of a 1:9:90 mixture of NH_4OH:MeOH:$CHCl_3$. Following flash chromatography on silica gel using 1:3:96

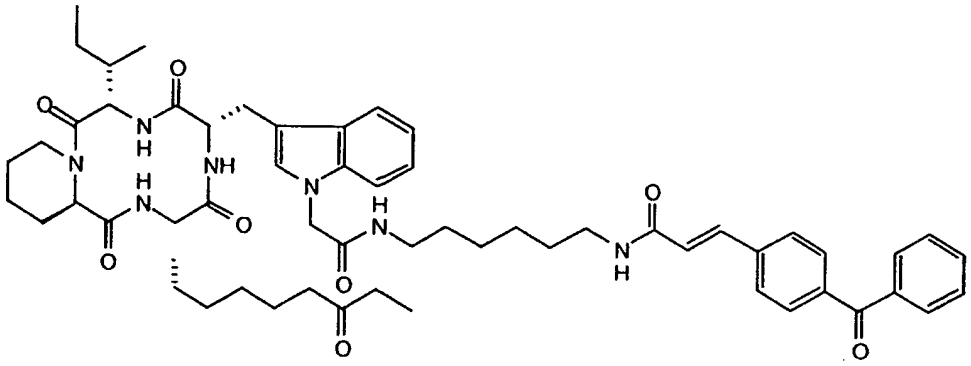
NH_4OH:MeOH:$CHCl_3$ as eluant, pure Example 87 was obtained without workup which was characterized by ^1H NMR.

EXAMPLE 88



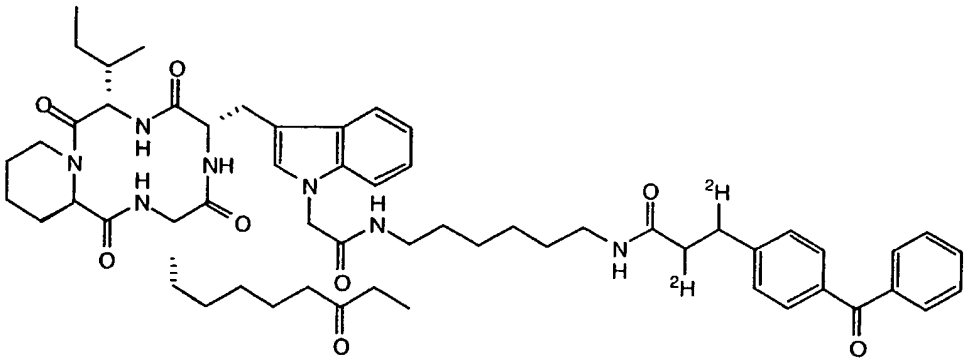
Example 88 was prepared by the following procedure. First, 6mg HOBT, 10mg (4-Bz)PhCO$_2$H, 23μL DIEA, and 19.6mg BOP were added to 250μL CH_2Cl_2 at RT to generate (4-Bz)PhCO(OBT). Then, 20μL of freshly prepared (4-Bz)PhCO(OBT) solution was added to 1mg N-desmethoxy-N-(6-aminohexylaminocarbonylmethyl)-apicidin in 200μL CH_2Cl_2 in a vial. The vial was wrapped in foil and allowed to stir at RT overnight. Partially purified product was obtained following preparative TLC on silica gel (1 x 250μm plate) using 1:9:90 NH_4OH:MeOH:$CHCl_3$ as eluant. Following preparative TLC on silica gel (1 x 250μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, pure Example 88 was obtained which was characterized by ^1H NMR. TLC: R_f = 0.27 (1:3:96 NH_4OH:MeOH:$CHCl_3$).

EXAMPLE 89



Example 89 was prepared by the following procedure. At RT, 3mg HOBT, 6μL Et_3N, and 4.1mg (4-Bz)PhCH=$CHCO_2H$ was added to 9mg N-desmethoxy-N-(6-aminohexylaminocarbonylmethyl)-apicidin in 1mL CH_2Cl_2 followed by 13mg BOP. After 4h, the crude was purified without workup by flash chromatography on silica gel using 1:3:96 NH_4OH:MeOH:$CHCl_3$. This yielded 13.4mg pure Example 89, which was characterized by ^1H NMR. TLC: $R_f = 0.29$ (1:3:96 NH_4OH:MeOH:$CHCl_3$). HPLC: $T_R = 4.90$min (7:3 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

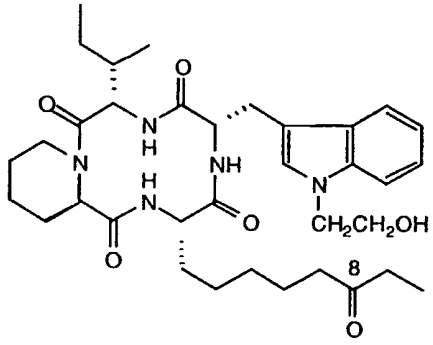
EXAMPLE 90



Example 90 was prepared by the following procedure. At RT, 3mg 5% Pd/C catalyst was added to 4mg Example 89 in 1:1 MeOH:CH_2Cl_2 and a deuterium gas atmosphere was established (balloon pressure). After 1h, the solution was purified on a silica gel pipette column using 1:9:90 NH_4OH:MeOH:$CHCl_3$ as eluant to yield 2.9mg pure Example 90, which was characterized by ^1H NMR. TLC:

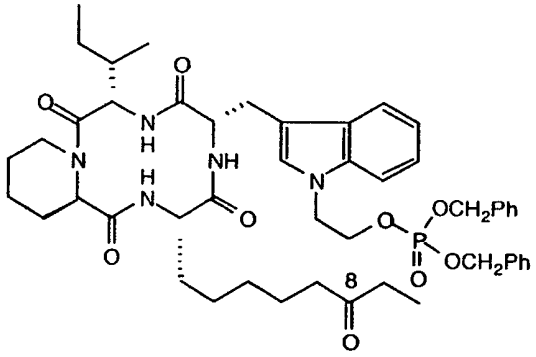
R_f = 0.34 (1:3:96 NH_4OH:MeOH:$CHCl_3$). HPLC: t_R = 4.66min (7:3 MeCN:H_2O, 1.5mL/min, Zorbax™ RX-8).

EXAMPLE 91



Example 91 was prepared by the following procedure. To 9mg of the silyl ether Example 74d in 0.2mL pyridine at 0°C was added 0.2mL HF•pyridine solution (prepared from 25g HF•pyridine, 10mL pyridine and 25mL THF). After 1.5h, the reaction was quenched by the addition of saturated $NaHCO_3$, extracted with CH_2Cl_2 and the combined organic layers were dried with Na_2SO_4. The 7.4mg of alcohol thus obtained was used in Example 92 below with no additional purification and was characterized by ^1H NMR and MS [m/z: 638 (M^++1)].

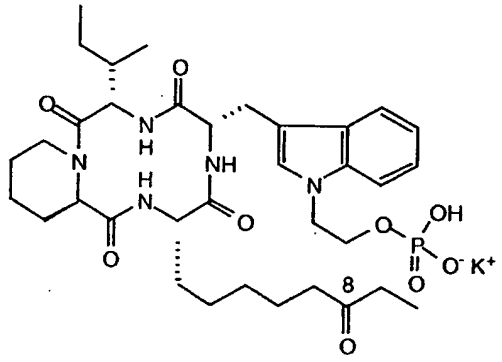
EXAMPLE 92



Example 92 was prepared by adding to 7.4mg of the Example 91 alcohol in 4mL CH_2Cl_2 at RT 422mg 1,2,4-triazolyle followed by 610μL $(PhCH_2O)_2PNEt_2$. After aging the solution for 3h, the volatiles were removed *in*

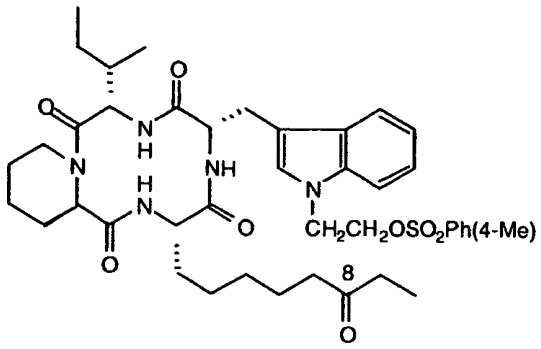
vacuo to form a yellow residue. Then, 7mL THF was added to the yellow residue to form a solution, which was cooled to -40°C. To this solution was added 4.6mL 30% H_2O_2 and warmed to RT. After aging for 30min, the reaction was quenched by the addition of 10% $Na_2S_2O_3$(aq), diluted with saturated $NaHCO_3$(aq) and water, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following chromatotron purification (1000μm plate) using 1:2 acetone:hexanes as eluant, 255mg pure Example 92 was obtained which was characterized by ^{1}H NMR and MS [m/z: 898 (M^++1)].

EXAMPLE 93



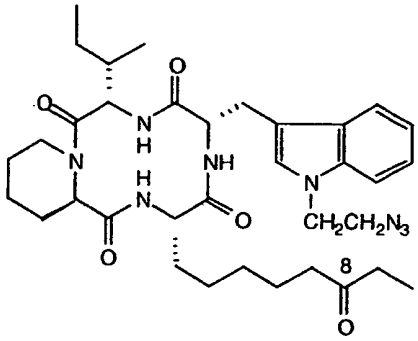
Example 93 was prepared by adding 27mg $KHCO_3$ and 25mg 10% Pd/C catalyst at RT to 245mg of Example 92 in 40mL *i*PrOH and 1mL water. An atmosphere of hydrogen (balloon pressure) was established for 12h. After the catalyst was removed by filtration through Celite using 1:1 MeOH:H_2O as eluant, the volatiles were removed under reduced pressure. No further purification was required and yielded 214mg Example 93, which was characterized by ^{1}H NMR and MS [m/z: 718 (M^++1)].

EXAMPLE 94



Example 94 was prepared by the following procedure. At 0°C, 2mg DMAP was added to 20mg apicidin alcohol in 2mL CH_2Cl_2 followed by the addition of 26mg Ts_2O. After 10min the solution was warmed to RT for 3h. Then, 10mg TsCl was added and the solution aged for 16h. The solvent was removed under reduced pressure and 1mg pure Example 94 was obtained following centrifugal TLC (4:6 acetone:hexanes to 1:9:90 NH_4OH:MeOH:$CHCl_3$) as eluant. The product was characterized by ^1H NMR and MS [m/z: 792 (M^++1)].

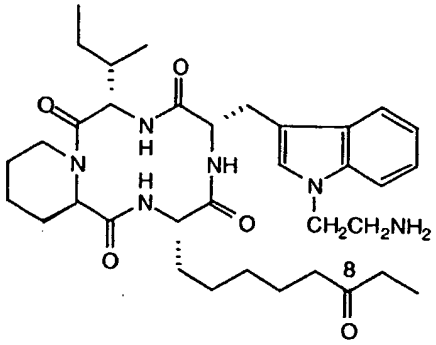
EXAMPLE 95



Example 95 was prepared by the following procedure. At 0°C, 247mg Ph_3P and 217mg $Zn(N_3)_3$•pyridine was added to 300mg N-desmethoxy-N-(2-hydroxyethyl)-apicidin in 25mL CH_2Cl_2, followed by the addition of 150µL DEAD. The solution was then warmed to RT. After aging for 12h, the volatiles were removed under reduced pressure. Following chromatotron TLC on silica gel (2mm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, 311mg pure Example 95 (Rf= 0.32, 1:9:90

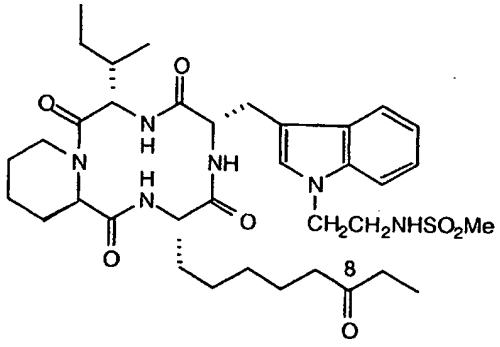
NH_4OH:MeOH:$CHCl_3$) was obtained which was characterized by ^1H NMR and MS [m/z: 663 (M^++1)].

EXAMPLE 96



Example 96 was prepared by the following procedure. At RT, 60mg 10% Pd/C catalyst was added to 311mg N-desmethoxy-N-(2-azidoethyl) apicidin in CH_2Cl_2 and an atmosphere of hydrogen was established (balloon pressure). After 8h, the catalyst was filtered through Celite using 3:7 *i*PrOH:$CHCl_3$ as eluant to yield the desired product. Following chromatotron PTLC (1 x 2000μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, pure Example 96 (200mg, R_f = 0.21 (1:3:96 NH_4OH:MeOH:$CHCl_3$) was obtained which was characterized by ^1H NMR and MS [m/z: 637 (M^++1)].

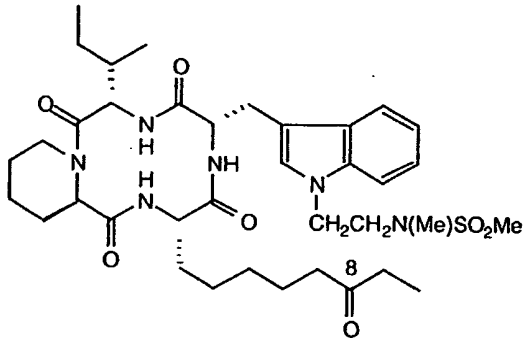
EXAMPLE 97



Example 97 was prepared by the following procedure. At 0°C, 9µL Et_3N was added to 10mg N-desmethoxy-N-(2-aminoethyl) apicidin in 0.5mL CH_2Cl_2

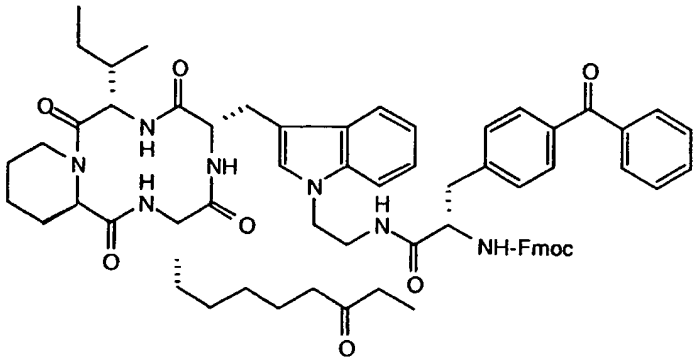
followed by the addition of 3.6μL $MeSO_2Cl$. The solution was warmed to RT and stirred for 30min. The solution was quenched by the addition of saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC (1 x 250μm plate) on silica gel using 1:1 acetone:hexanes as eluant, 9mg pure Example 97 was obtained which was characterized by ^1H NMR and MS [m/z: 732.7 (M+ NH_4)]. TLC: R_f = 0.26 (1:1 acetone:hexanes). HPLC: t_R = 4.7 min (1:1 MeCN:H_2O, 1.5 ml/min, Zorbax™ RX-C8).

EXAMPLE 98



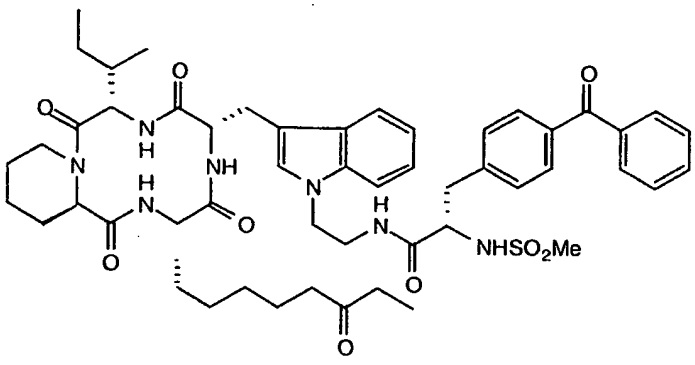
Example 98 was prepared by the following procedure. At RT, 7 μL $NaN(TMS)_2$ (1M in THF) was added to 4mg N-desmethoxy-N-2-methanesulfonamidoethyl apicidin in 0.28mL THF followed by the addition of 1.5μL MeI. After 16h, the solution was quenched by the addition of water, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC (1 x 250μm plate) on silica gel using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, 2.2mg pure Example 98 was obtained which was characterized by ^1H NMR and MS [m/z; 746.6 (M^++NH_4)]. TLC: R_f = 0.42 (1:3:96 NH_4OH:MeOH:$CHCl_3$).

EXAMPLE 99



Example 99 was prepared by the following procedure. At RT, 5mg HOBT, 7μL TEA and 18.4mg Fmoc-Phe(4-Bz)-OH was added to 16mg N-desmethoxy-N-(2-aminoethyl)-apicidin in 1mL CH_2Cl_2 followed by the addition of 16mg BOP. After 3h at RT, the solution was purified by flash chromatography on silica gel using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant to yield pure Example 99, which was characterized by ^1H NMR. TLC: $R_f = 0.50$ (1:3:96 NH_4OH:MeOH:$CHCl_3$).

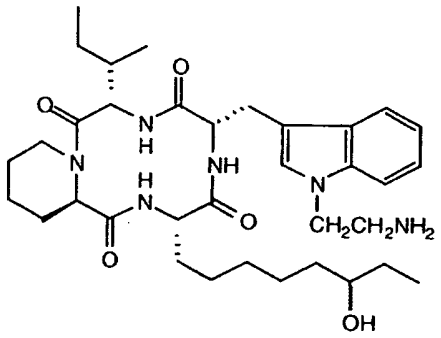
EXAMPLE 100



Example 100 was prepared by adding 50μL piperidine to 15mg of the Fmoc-protected amine of Example 99 at RT in 2mL CH_2Cl_2. After 2h at RT, the solution was concentrated under reduced pressure and lyophilized from dioxane to remove residual piperidine. The crude deprotected amine product was dissolved in 2mL CH_2Cl_2 at 0°C and 5.6μL Et_3N was added followed by 62μL $MeSO_2Cl$ (0.26M in CH_2Cl_2). After 1h, the reaction was quenched by the addition of saturated

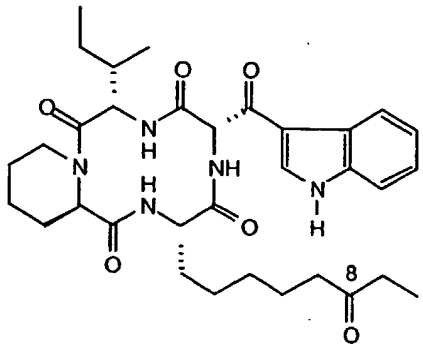
$NaHCO_3$(aq), extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC on silica gel (1 x 1000μm plate) using 1:4:95 NH_4OH:MeOH:$CHCl_3$ as eluant, pure Example 100 was obtained which was characterized by ^1H NMR and MS [m/z: 1080 (M^++1)].

EXAMPLE 101



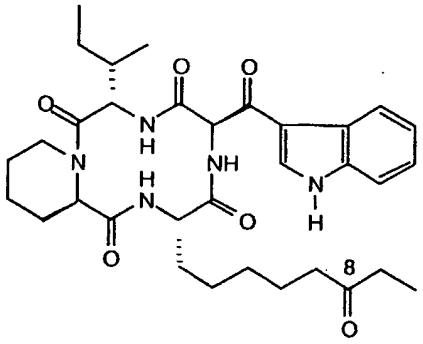
Example 101 was prepared by the following procedure. At RT, 8mg $NaBH_4$ was added to 20mg N-desmethoxy-N-(2-aminoethyl) apicidin in 2mL MeOH. After 2h at RT, acetone was added to the solution to quench the reaction and the solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following flash chromatography on silica gel using 1:9:90 NH_4OH:MeOH:$CHCl_3$ as eluant, pure Example 101 was obtained which was characterized by ^1H NMR. TLC: Rf = 0.28 (1:9:90 NH_4OH:MeOH:$CHCl_3$).

EXAMPLE 102



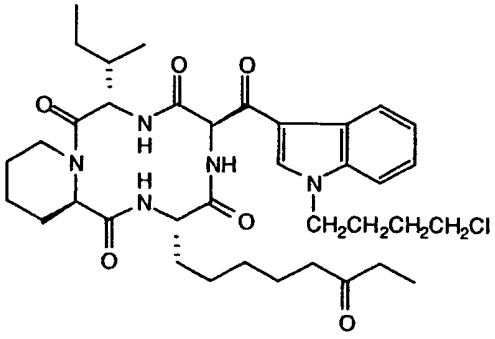
Example 102 was prepared by the following procedure. At RT, 16.1mg DDQ was added to 20mg N-desmethoxy apicidin in 1.1mL 9:1 MeCN:H_2O to form a dark purple solution, which became blood-red over 30 min. The solution was aged at 0°C for 12h. The solution was purified without workup by RP-HPLC using 4:6 MeCN:H_2O as eluant. This yielded 15mg of Example 102 which was characterized by ^1H NMR and MS [m/z: 608 (M^++1)].

EXAMPLE 103

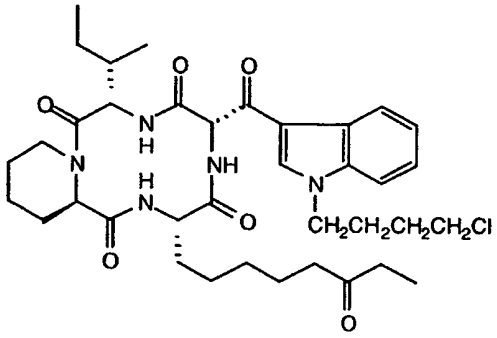


Example 103 was prepared by the following procedure. At RT, 1.5µL Et_3N was added to 6mg *cyclo*(beta-oxo-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 0.5mL CH_2Cl_2. After 10min, the solution was purified without workup by RP-HPLC using 1:1 MeCN:H_2O as eluant. This yielded 3mg pure Example 103, which was characterized by ^1H NMR and MS [m/z: 608 (M^++1)].

EXAMPLES 104A AND 104B



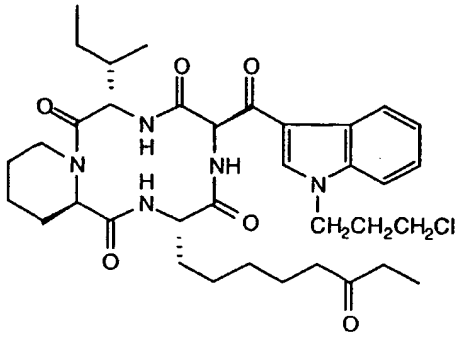
Ex. 104a



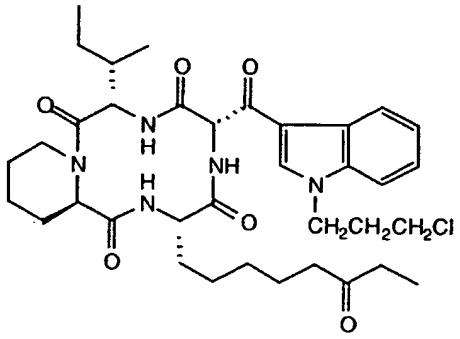
Ex. 104b

Examples 104a and 104b were prepared by the following procedure. At RT, 0.14mL $BrCH_2CH_2CH_2CH_2Cl$, 0.5g nBu4NI and 25mg 95% NaH were added to 300mg beta-oxo-N-desmethoxy apicidin in 0.5mL DMF containing 0.25mL HMPA. The solution was degassed with bubbling N_2 for 4min and then heated to 100°C for 90min. The solution was then cooled to RT, poured into saturated brine/saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC (2 x 1500μm plates) on silica gel using 1:3:96 NH_3:MeOH:$CHCl_3$ as eluant, a pure mixture of Example 104a and Example 104b was obtained. The pure products were characterized by ^{1}H NMR and MS [m/z: 698.5 (M+1) for each isomer]. The yield was 150mg D-Trp isomer and 120mg L-Trp isomer. TLC: R_f = 0.42 for D-Trp isomer and 0.25 for L-Trp isomer (2:3 acetone:hexanes).

EXAMPLES105A AND 105B



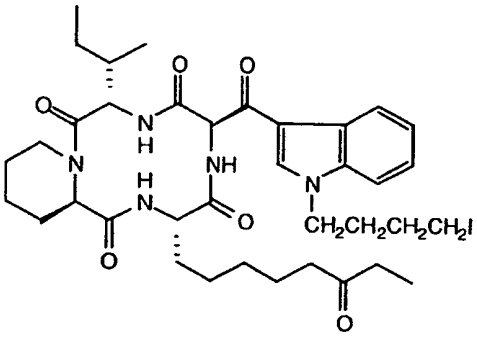
Ex. 105a



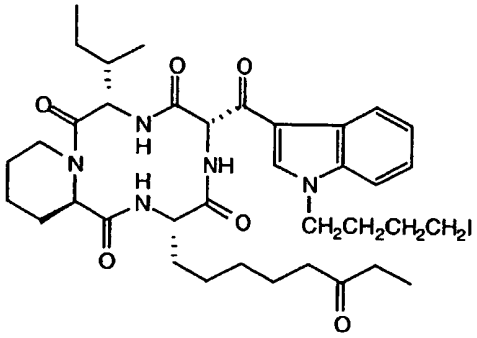
Ex. 105b

Examples 105a and 105b were prepared by adding 0.12mL $BrCH_2CH_2CH_2Cl$, 0.5g *n*Bu_4NI and 25mg 95% NaH at RT to 300mg beta-oxo-N-desmethoxy apicidin in 0.5mL DMF containing 0.25mL HMPA. The solution was degassed with bubbling N_2 for 4min and then heated to 100°C for 90min. The solution was cooled to RT, poured into 1:1 saturated brine:saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC (2 x 1500μm plates) on silica gel using 1:3:96 NH_3:MeOH:$CHCl_3$ as eluant, a pure mixture of Examples 105a and 105b were obtained which were characterized by ^{1}H NMR and MS [m/z: 684.5 (M^++1) for each isomer]. Yield: 120mg D-Trp isomer and 80mg L-Trp isomer. TLC: R_f = 0.55 for D-Trp isomer and 0.27 for L-Trp isomer (2:3 acetone:hexanes).

EXAMPLES 106A AND 106B



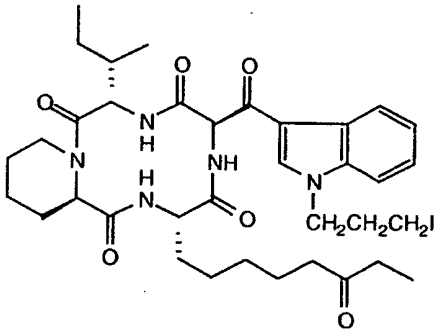
Ex. 106a



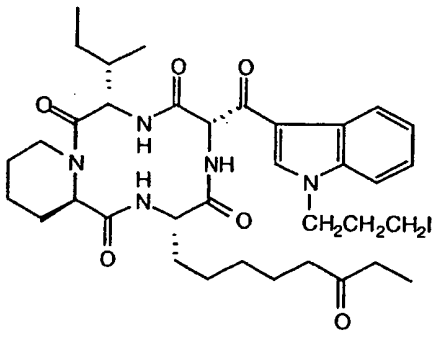
Ex. 106b

Examples 106a and 106b were prepared by adding 516mg NaI to 120mg *cyclo*(N-(4-chloro-n-butyl)-beta-oxo-D-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 2.2mL anhydrous MeCN. The resulting solution was heated to 60°C for 12h. The solution was cooled to RT and diluted with 1:1 brine:saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. This yielded 100mg of a mixture of Example 106a and 106b which was characterized by ^1H NMR and MS [m/z: 790.5 (M^++1) for each isomer] without purification. TLC: R_f = 0.58 for D-Trp isomer and 0.41 for L-Trp isomer (1:3:96 NH_4:MeOH:$CHCl_3$)

EXAMPLES 107A AND 107B



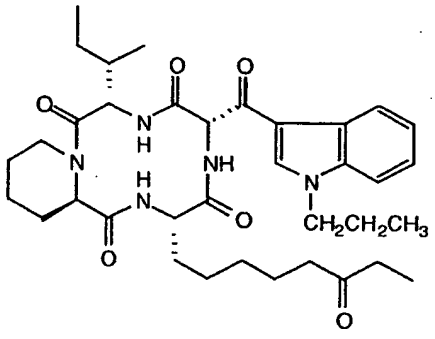
Ex. 107a



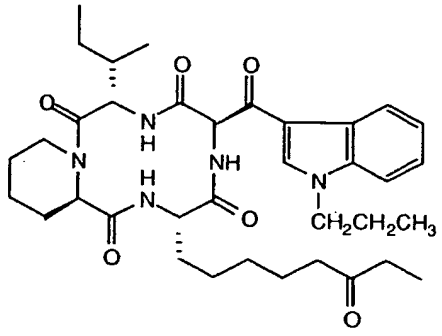
Ex. 107b

Examples 107a and 107b were prepared by adding 350mg NaI to 80mg *cyclo*(N-(4-chloro-n-propyl)-beta-oxo-D-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 1.5mL anhydrous MeCN. The resulting solution was heated to 60°C for 12h. The solution was cooled to RT, diluted with 1:1 brine:saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. This yielded 70mg of a mixture of Example 107a and Example 107b which were characterized by ^1H NMR and MS [m/z: 776.5 (M^++1) for each isomer] without purification. TLC: R_f = 0.53 for D-Trp isomer and 0.42 for L-Trp isomer (1:3:96 NH_4OH:MeOH:$CHCl_3$).

EXAMPLES 108A AND 108B



Ex. 108a

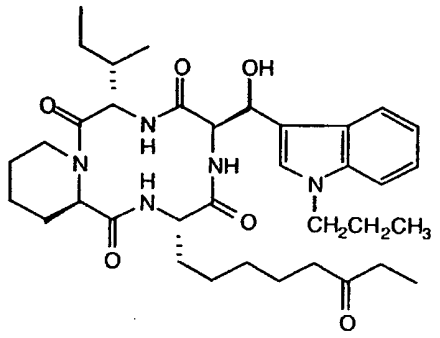


Ex.108b

Examples 108a and 108b were prepared by adding 30mg $MgBr_2$•Et_2O, and 30µL *n*Bu_3SnH to 40mg of an ~1:1 mixture of *cyclo*(N-(3-iodo-n-propyl)-beta-oxo-D-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) and *cyclo*(N-(3-iodo-n-propyl)-beta-oxo-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 0.5mL CH_2Cl_2. The resulting solution was cooled to -78°C. Next, 100µL Et_3B was added followed by 500µL oxygen gas via syringe over 2h. The reaction was quenched by the addition of 1:1 brine:saturated $NaHCO_3$ at -78°C. The solution was then warmed to RT, partitioned with CH_2Cl_2 and the organic layer dried with Na_2SO_4. The solution was concentrated under reduced pressure and the residue partitioned between hexanes:MeCN (1:3). The MeCN layer was washed (3x) with hexanes and the MeCN layer concentrated under reduced pressure. Pure products were obtained following PTLC (1 x 1000µm plate) on silica gel using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant. Pure products were characterized by ^1H NMR and MS [m/z: 650.6 (M^++1) for each

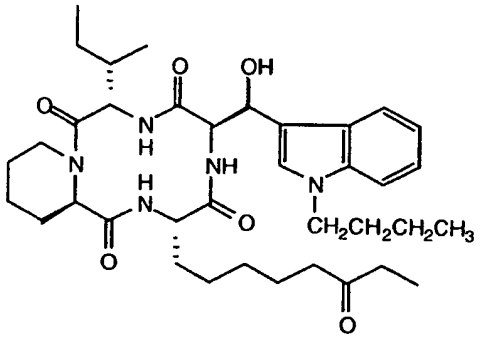
isomer]. Yield: 14mg D-Trp isomer and 14mg L-Trp isomer. TLC: R_f = 0.69 for D-Trp isomer and 0.51 for L-Trp isomer (1:3:96 NH_4OH:MeOH:$CHCl_3$).

EXAMPLE 109



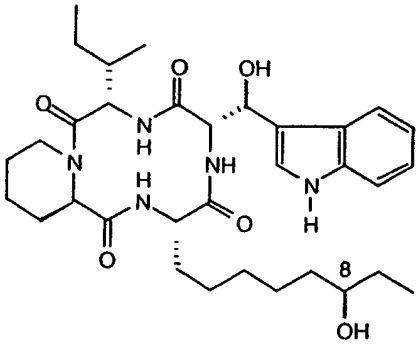
Example 109 was prepared by the following procedure. At RT, 5mg 2,2'-azobisisobutyronitrile and 38μL *n*Bu3SnH were added to a 22mg mixture of *cyclo*(N-(3-iodo-n-propyl)-beta-oxo-D-(and L, ~1:1)-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 0.6mL toluene. Nitrogen was bubbled through the solution for 5min and it was then heated to 100°C for 2h. The solution was cooled to RT, concentrated under reduced pressure and the residue partitioned between hexanes:MeCN (1:3). The MeCN layer was washed (3x) with hexanes and the MeCN layer concentrated under reduced pressure. Following PTLC on silica gel using 4:6 acetone:hexanes as eluant, 10mg pure Example 109 was obtained which was characterized by ^1H NMR and MS [m/z: 652.7 (M^++1)]. TLC: R_f = 0.50 and 0.43 (mixture of beta-hydroxy isomers) (1:3:96 NH_4OH:MeOH:$CHCl_3$).

EXAMPLE 110

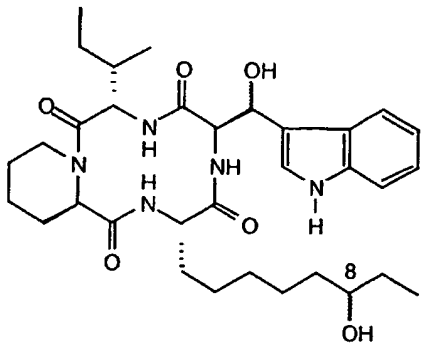


Example 110 was prepared by the following procedure. At RT, 6mg 2,2'-azobisisobutyronitrile and 52μL *n*Bu3SnH was added to 31mg of a ~1:1 mixture of *cyclo*(N-(4-iodo-n-butyl)-beta-oxo-D-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) and *cyclo*(N-(4-iodo-n-butyl)-beta-oxo-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 0.8mL toluene. Nitrogen was bubbled through the solution for 5min and it was then heated to 100°C for 2h. The solution was cooled to RT, concentrated under reduced pressure and the residue partitioned between hexanes:MeCN (1:3). The MeCN layer was washed (3x) with hexanes and the MeCN layer concentrated under reduced pressure. Example 110 was characterized by ^{1}H NMR without purification. TLC: R_f = 0.66 (1:3:96 NH_4OH:MeOH:$CHCl_3$).

EXAMPLES 111A AND 111B



Ex. 111a

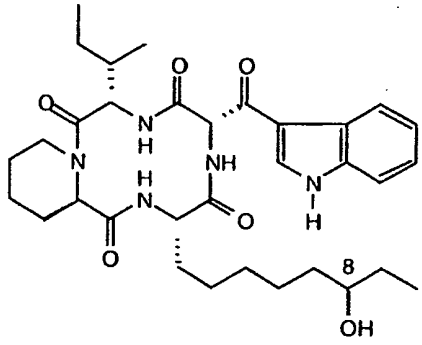


Ex. 111b

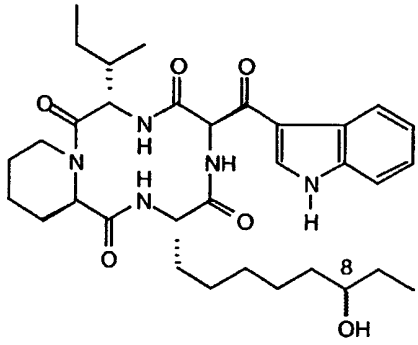
Examples 111a and 111b were prepared by adding 1mg $NaBH_4$ to 3mg beta-oxo-N-desmethoxy apicidin in 0.25mL EtOH at 0°C. After 2.5h at RT and 10h

at 0°C, the solution was poured into saturated NH_4Cl, extracted with 3:1 EtOAc:*i*PrOH and dried with Na_2SO_4. Following RP-HPLC using gradient elution (2:3 to 1:1 MeCN:H_2O), a mixture of pure Example 111a and 111b were obtained which was characterized by ^1H NMR and MS [m/z: 594 (M^+-H_2O) for both isomers]. TLC: R_f = 0.50 for D-Trp isomer and 0.28 for L-Trp isomer (1:9:90 NH_4OH:MeOH:$CHCl_3$). HPLC: t_R = 3.9min for D-Trp isomer and 3.5min for L-Trp isomer (1:1 MeCH:H_2O, 1.5mL/min, Zorbax™ RX-C8).

EXAMPLES 112A AND 112B



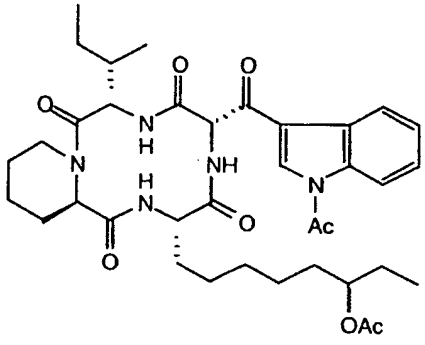
Ex. 112a



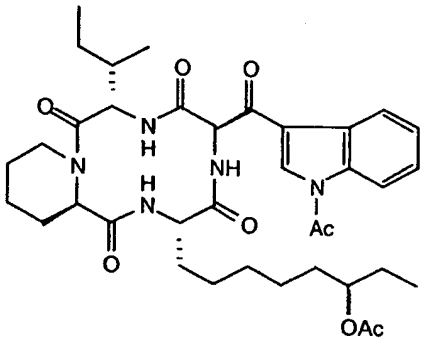
Ex.112b

Examples 112a and 112b were prepared by adding 5.8mg $CeCl_3 \cdot 6H_2O$ to 10mg *cyclo*(beta-oxo-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) at RT in 0.2mL MeOH. After 5min, the solution was cooled to 0°C and 0.6mg $NaBH_4$ was added. The solution was poured into saturated NH_4Cl, extracted with EtOAc and dried with Na_2SO_4. Following RP-HPLC using 1:1 MeCN:H_2O as eluant, a pure mixture of 0.7mg Example 112a and 1.3mg Example 112b was obtained which was characterized by ^1H NMR and MS [m/z: 609 (M^++1) for each isomer].

EXAMPLES 113A AND 113B



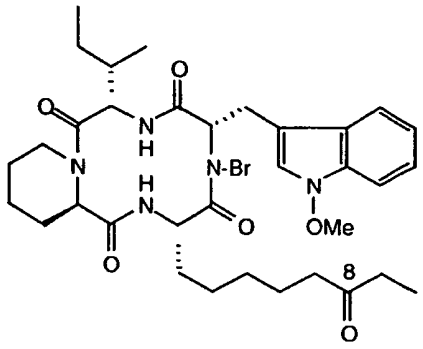
Ex. 113a



Ex. 113b

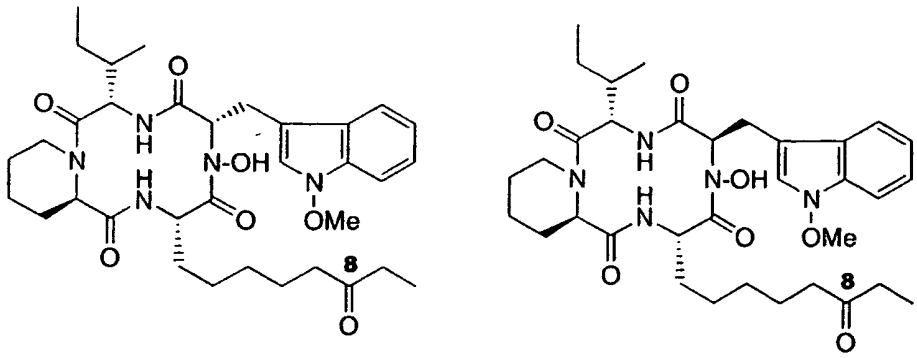
Examples 113a and 113b were prepared by adding 14mg DMAP and 0.533mL Ac_2O to 700mg *cyclo*(beta-oxo-L-Trp-L-Ile-D-Pip-L-2-amino-8-hydroxy-decanoyl) in 115mL dichloroethane at RT. After 8h, the mixture was poured into saturated NH_4Cl, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following preparative chromatotron (4μm plate) on silica gel using 2:8 to 4:6 acetone:hexanes gradient elution as eluant, 8mg of a mixture of Examples 113a and 113b was obtained. Pure epimeric products were characterized by ^1H NMR and MS. D-Trp isomer: yield: 140mg; TLC: R_f = 0.71 (1:1 acetone:hexanes); MS [m/z: 694.4 (M^++1)]. L-Trp isomer: yield: 110mg; TLC: R_f = 0.57 (1:1 acetone:hexanes); MS [m/z: 694.5 (M^++1)].

EXAMPLE 114



Example 114 was prepared by the following procedure. At RT, 28.5mg N-bromosuccinamide and 1.2mg benzoyl peroxide was added to 100mg apicidin in 5.3mL CCl_4. Nitrogen then was bubbled through the solution for 5min. The solution was refluxed for 15min and then cooled to RT. Following PTLC on silica gel (3 x 1000μm plates) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ (one development) followed by 4:6 acetone:hexanes (two developments) as eluant, 62mg pure Example 114 was obtained which was characterized by ^1H NMR and MS [m/z: 704 (M^++1)]. RP-HPLC: t_R = 5.02 min (apicidin: t_R = 4.82min), 6:4 MeCN:H_2O, 1.5mL/min.

EXAMPLES 115A AND 115B



Ex. 115a **Ex. 115b**

Example 115a (mobile product A) and Example 115b (polar product B) were prepared by the following methods E and F.

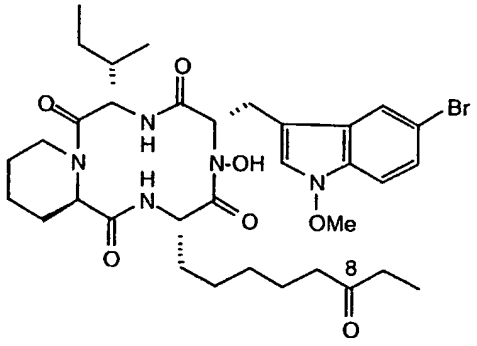
Method E

At 0°C, 10mg Example 114 was added to 4mg $AgBF_4$ in 250μL 3:1 DMSO:CH_2Cl_2. After aging for 10min (at this point, TLC showed the disappearance of the starting bromide), 10μL Et_3N was added and the solution aged for an additional hour. The reaction was quenched by the addition of water. The mixture was then extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC on silica gel (1 x 250μm plate) using 1:1 acetone:hexanes as eluant, a pure mixture of Examples 115a and 115b was obtained which were characterized by ^1H NMR and MS [m/z: 640 (M^++1) for both isomers]. TLC: Rf= 0.48 Example 115a (mobile product A) and 0.41 Example 115b (polar product B), 1:1 acetone:hexanes.

Method F

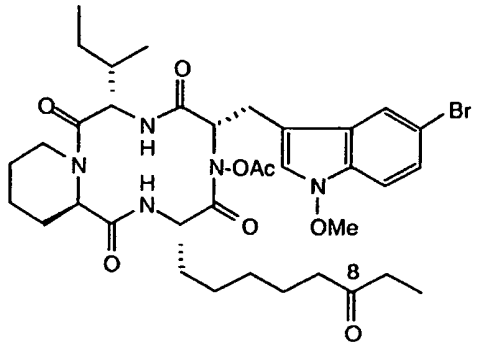
At RT, 12mg $NaHCO_3$ was added to 43mg apicidin in CH_2Cl_2, followed by 18mg 85% MCPBA. The resulting solution was vigorously stirred for 12h. The solution was then poured into saturated $NaHCO_3$(aq), extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC on silica gel (1 x 250μm plate) using 1:1 acetone:hexanes, pure Example 115a was obtained which was identical in all respects to Example 115a, mobile product A, from Method E above.

EXAMPLE 116



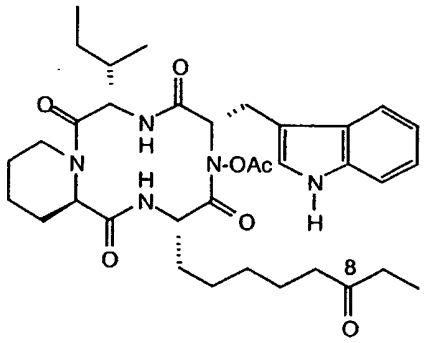
Example 116 was prepared by following the general procedure of Example 115a, method E. Starting with 10mg of Example 114, 4mg of Example 116 was prepared which was characterized by ^1H NMR and MS [m/z: 718.6 (M^++1)].

EXAMPLE 117



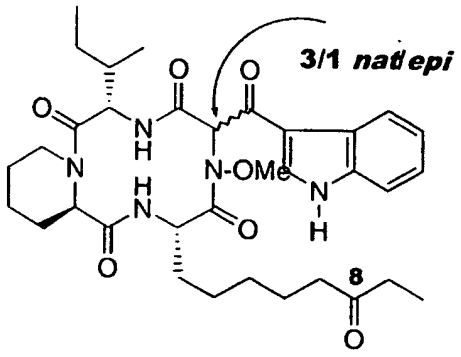
Example 117 was prepared by adding 4μL Ac_2O to 5.4mg of Example 115b at RT in 375μL $ClCH_2CH_2Cl$, followed by the addition of 0.3mg DMAP. After 1.5h, the volatiles were removed under a stream of nitrogen. Following PTLC on silica gel (1 x 250μm plate) using 1:1 acetone:hexanes as eluant, 6mg pure Example 117 which was characterized by ^1H NMR and MS [m/z: 762 (M^++1)].

EXAMPLE 118



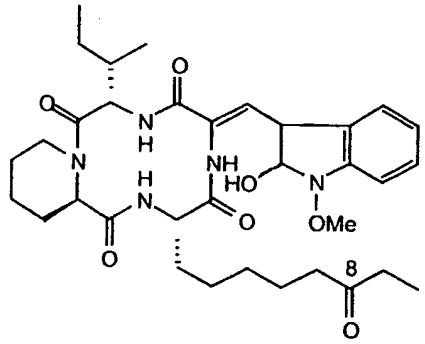
Example 118 was prepared by the following procedure. To 5mg of Example 117 at RT in 1mL CH_2Cl_2 was added 1mg $Pd(OH)_2$ and a hydrogen atmosphere was established (balloon pressure). After aging for 2h, the solution was filtered and concentrated under reduced pressure. Following flash chromatography on silica gel using 1:9:90 NH_4:MeOH:$CHCl_3$, 3.5mg pure Example 118 was obtained which was characterized by ^1H NMR and MS [m/z: 652 (M^++1)].

EXAMPLE 119



Example 119 was prepared by the following procedure. To 25mg beta-oxo-N-desmethoxy-apicidin at RT in 1.5mL MeOH was added 15µL pyridine followed by the addition of 126mg $Pb(OAc)_4$. After aging for 48h, the solution was cooled to 0°C and saturated $Na_2S_2O_3$(aq) was added. The solution was poured into saturated NH_4Cl(aq):brine (1:1), extracted with *i*PrOH:$CHCl_3$ (3:7) and dried with Na_2SO_4. The solution was filtered and concentrated under reduced pressure. Following flash chromatography on silica gel using 1:9:90 NH_4:MeOH:$CHCl_3$, 36mg pure Example 119 was obtained which was characterized by ^1H NMR and MS [m/z: 638 (M^++1)].

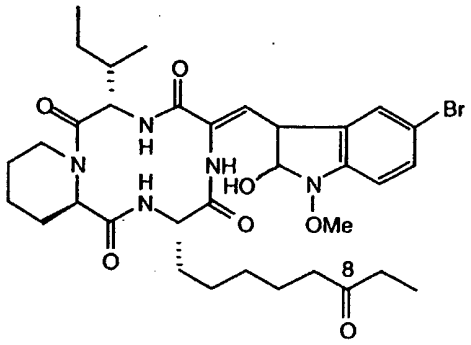
EXAMPLE 120



Example 120 was prepared by the following procedure. To 81mg of Example 114 in 6mL THF:H_2O at RT was added 141mg basic Al_2O_3 and 191mg Ag_2CO_3. The solution was warmed to 50°C for 5h, then cooled to RT. The mixture

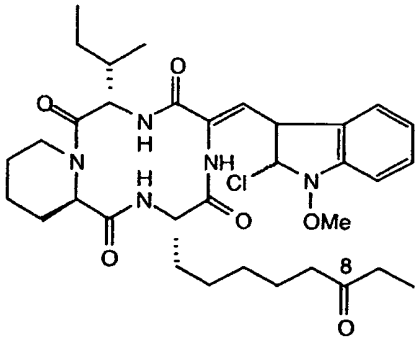
was partitioned between water and CH_2Cl_2, the layers separated, the organic layer dried with Na_2SO_4 and then filtered through Celite. Following PTLC (1 x 500μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, pure Example 120 was obtained which was characterized by ^{1}H NMR and MS [m/z: 640.5 (M^++1)].

EXAMPLE 121



Example 121 was prepared by following the general procedure of Example 120, and utilizing the dibromide Example 126 as the starting material. The product thus obtained was characterized by ^{1}H NMR and MS [m/z: 720 (M^++1)].

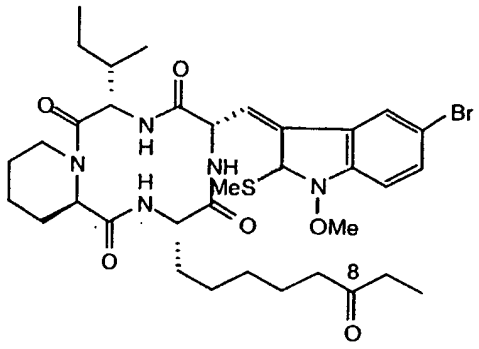
EXAMPLE 122



Example 122 was prepared by the following procedure. To 200μL CH_2Cl_2 at -78°C was added 6μL oxallyl chloride (2M solution in CH_2Cl_2) followed by the addition of 2μL DMSO. After 5min, 3.3mg of Example 120 (as a solution in 50μL CH_2Cl_2) was added to the DMSO/oxallyl chloride solution. After aging for 15min, 14μL Et_3N was added and the solution was warmed to 0°C. The reaction was

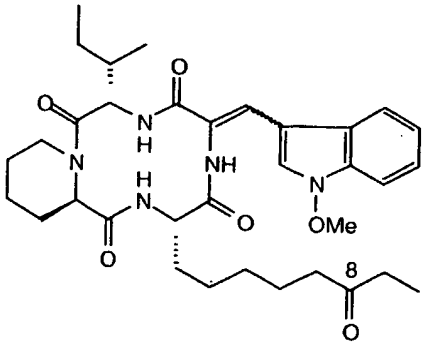
then quenched by the addition of water, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC on silica gel (1 x 500μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, pure Example 122 was obtained which was characterized by ^1H NMR and MS [m/z: 658 (M^++1)].

EXAMPLE 123



Example 123 was prepared by mixing 28mg of Example 126 in 1.5mL DMF at RT with 13mg NaSMe. The mixture was then warmed to 50°C. After 1h, the solution was poured into water, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC purification on silica gel (1 x 250μm plate) using 4:6 acetone:hexanes as eluant (two developments). Pure Example 123 was obtained which was characterized by ^1H NMR and MS [m/z: 748 (M^++1)].

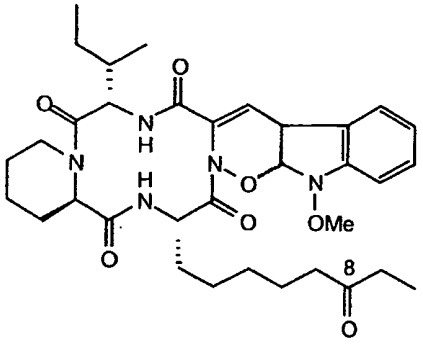
EXAMPLE 124



Example 124 was prepared by adding 5.4mg KSAc to 11mg of Example 114 in 260μL DMF at 0°C. After aging the solution for 48h, it was warmed

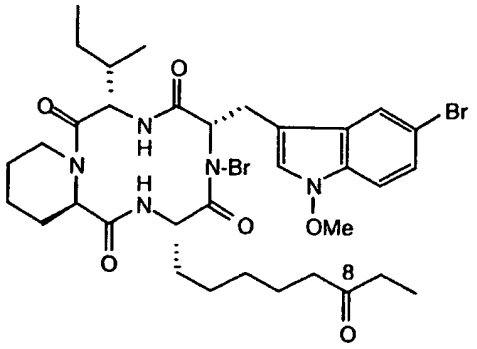
to RT and aged an additional 20h. The solution was poured into water, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC on silica gel using 4:6 acetone:hexanes as eluant, the product thus obtained was characterized by ^1H NMR and MS [m/z: 622 (M^++1)].

EXAMPLE 125



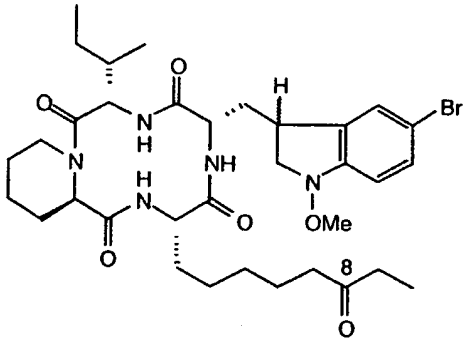
Example 125 was prepared by adding 5mg DDQ to 5mg of Example 115a (mobile product A) at RT in 200μL THF. The resulting solution was warmed to 65°C. After aging for 20h, an additional 5mg DDQ was added. After an additional 6h, the volatiles were removed at ambient temperature under reduced pressure. Methylene chloride was added, the solution was filtered and the filtrate was loaded onto a preparative TLC plate (1 x 250μm plate, silica gel). Following PTLC purification using 4:6 acetone:hexanes as eluant, the pure Example 125 thus obtained was characterized by ^1H NMR and MS [m/z: 608.6 (M^++1)].

EXAMPLE 126



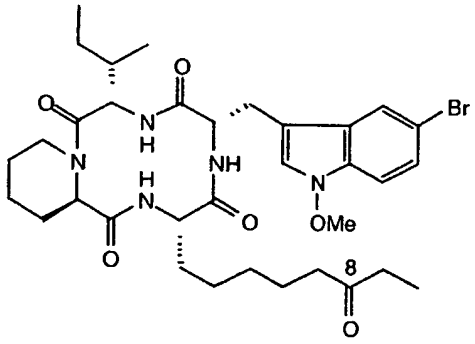
Example 126 was prepared by the following procedure. At RT, 86mg N-bromosuccinamide was added to 100mg apicidin in 5.3mL CCl_4, followed by the addition of 1.2mg benzoyl peroxide. The resulting solution was purged with vigorous nitrogen bubbling for 5min. The solution was heated to reflux for 45min and then cooled to RT. The volatiles were removed under reduced pressure and pure Example 126 was obtained following PTLC purification on silica gel (1500μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant. The dibromide Example 126 product thus obtained was characterized by ^1H NMR and MS [m/z: 780 (M^++1)]. TLC: R_f= 0.49 (1:3:96 NH_4OH:MeOH:$CHCl_3$). HPLC: t_R = 10.02min, 1mL/min, 6:4 MeCN:H_2O, Zorbax™ RX-8).

EXAMPLES 127A AND 127B



Mobile product A

Ex. 127a



Polar product B

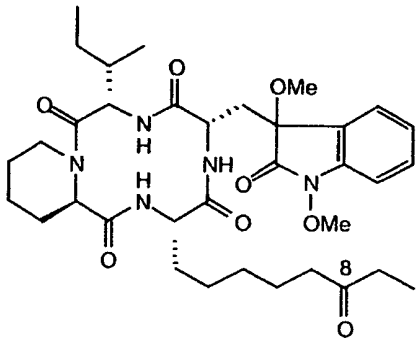
Ex. 127b

Examples 127a and 127b were prepared by adding 0.32mL DMF, and 0.32mL 1:1 saturated $NaHCO_3$:H_2O to 10mg of Example 126, followed by the addition of 4.5mg $Na_2S_2O_4$. The milky white solution thus formed was aged at RT for 24h. Then, 2mL Acetonitrile was added, and the solids were removed by filtration. This yielded 1mg pure Example 127a (mobile product A) and 4mg pure Example 127b (polar product B) following RP-HPLC using 1:1 MeCN:H_2O as eluant. Both products were characterized by ^1H NMR and MS.

Example 127a, mobile product A: MS: [m/z: 704 (M^++1)]; TLC: R_f = 0.75 (1:1 acetone:hexanes); HPLC: t_R = 8min, 2mL/min, 1:1 MeCN:H_2O, Zorbax™ RX-8).

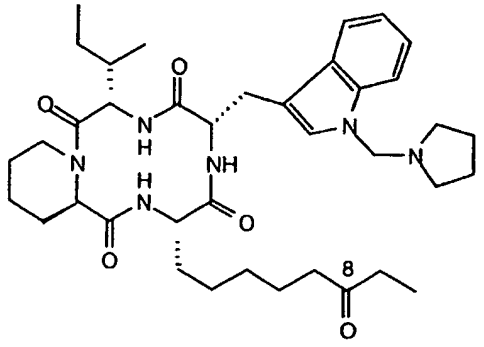
Example 127b, polar product B: MS: [m/z: 702 (M^++1)]; TLC: R_f= 0.60 (1:1 acetone:hexanes); HPLC: t_R = 7min, 2mL/min, 1:1 MeCN:H_2O, Zorbax™ RX-8).

EXAMPLE 128

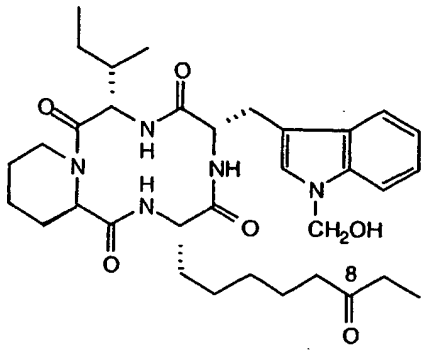


Example 128 was prepared by the following procedure. At 0°C, 6mg N-bromosuccinamide was added to 13mg apicidin in 1mL CH_2Cl_2 and 0.5mL MeOH. After 4min, 1mL saturated Na_2SO_3(aq) was added, followed by 1mL brine. The solution was extracted with EtOAc and dried with Na_2SO_4. Partially purified product was obtained following PTLC on silica gel (1 x 1500μm plate) using 1:2 acetone:hexanes as eluant. Pure Example 128 was subsequently obtained following flash chromatography on silica gel using 1:2 acetone:hexanes as eluant. The Example 128 thus obtained was characterized by ^1H NMR and MS [m/z: 670.4 (M^++1)].

EXAMPLES 129A AND 129B



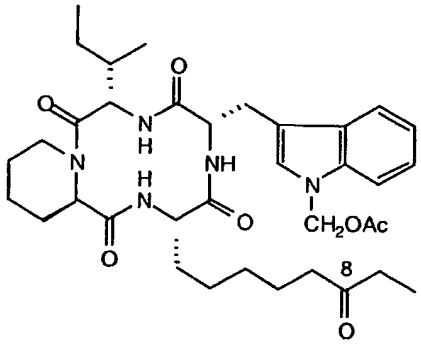
Ex. 129a



Ex. 129b

Examples 129a and 129b were prepared by the following procedure. To 10mg N-desmethoxy apicidin at RT in 0.1mL DMF was added 3μL 37% formaldehyde(aq) and 3μL pyrrolidine. After 48h, the reaction was quenched with saturated $NaHCO_3$, extracted with EtOAc and dried with Na_2SO_4. Pure 2mg of the pyrrolidino Example 129a (Rf= 0.2) and 2mg of the hydroxymethyl Example 129b (Rf= 0.1) was obtained following PTLC (1:3:96 NH_4OH:MeOH:$CHCl_3$, Rf= 0.2) as eluant. The pure products were characterized by ^1H NMR and MS [m/z: 624 (M^++1) for the pyrrolidino Example 129a and 677 (M+1) for the hydroxymethyl Example 129b].

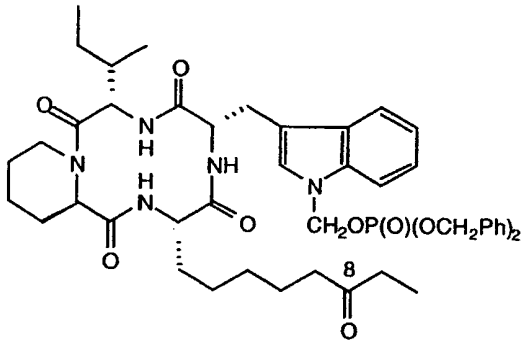
EXAMPLE 130



Example 130 was prepared by the following procedure. To 5mg N-desmethoxy-N-hydroxymethyl apicidin in 0.16mL pyridine at RT was added 0.63mL

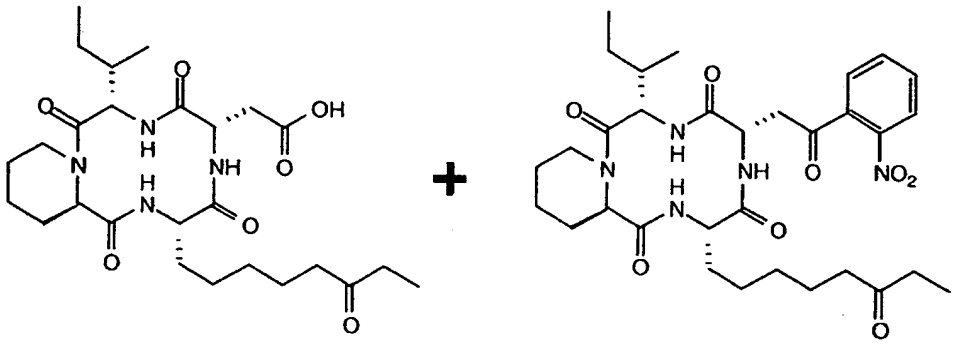
acetyl chloride and one crystal of DMAP. After 12h, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc and dried with Na_2SO_4. Following RP-HPLC using a linear gradient of 4:6 to 1:0 MeCN:H_2O as eluant, pure Example 130 was obtained which was characterized by ^1H NMR and MS [m/z: 666 (M^++1)].

EXAMPLE 131



Example 131 was prepared by the following procedure. To 9mg N-desmethoxy-N-hydroxymethyl apicidin in CH_2Cl_2 at 0°C was added 13μL $EtN(iPr)_2$ followed by the addition of 43μL $(PhCH_2O)_2P(O)Cl$. After 30min at 0°C, 0.4mg DMAP was added and the solution was aged for 1.5h at 0°C, followed by 2.5h at RT. The reaction was quenched by the addition of water, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following preparative RP-HPLC using a linear gradient of 4:6 Æ 1:0 MeCN:H_2O as eluant, 0.3mg pure Example 131 was obtained which was characterized by ^1H NMR and MS [m/z: 884 (M+1)].

EXAMPLES 132A AND 132B



Ex. 132a **Ex. 132b**

Examples 132a and 132b were prepared by the following methods G, H and I.

Method G

To 100mg apicidin in 4mL MeCN and 3mL CH_2Cl_2 at RT was added 800mg $NaIO_4$ in 10mL water, followed by the addition of 10mg $RuCl_3$. The solution was then aged overnight. The solution was poured into brine, acidified with glacial acetic acid and filtered to remove particulates. The solids were rinsed with CH_2Cl_2 and the solution was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Pure 52mg carboxylic acid Example 132a was obtained following preparative RP-HPLC using gradient elution (1:4 to 1:1 MeCN:H_2O, 50min linear ramp). Example 132a obtained was characterized by ^1H NMR and MS [m/z: 523.2 (M^++1)]. Also obtained from this reaction was the nitrophenylketone apicidin analog, Example 132b, which was characterized by ^1H NMR and MS [m/z: 628.2 (M^++1)].

Method H

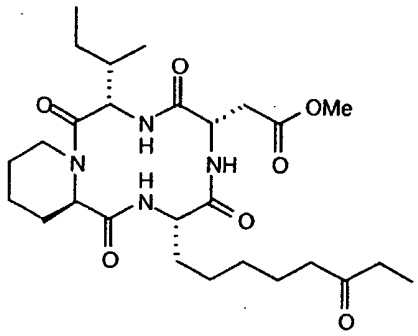
To a solution containing 0.3mg $RuCl_3 \cdot xH_2O$ and 50mg N-desmethoxy apicidin in 2mL 1:1 MeCN:CCl_4 was added 324mg $NaIO_4$ (as a solution in 1mL H_2O). After 45h, the resulting green solution was partitioned between 1:1 brine:saturated NH_4Cl and 3:7 *i*PrOH:$CHCl_3$. The organic layer then was dried with

Na_2SO_4. The solution was concentrated under reduced pressure to yield 60mg crude product.

Method I

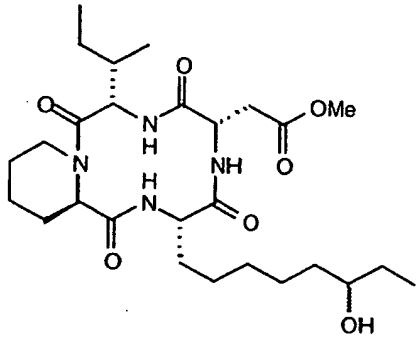
To 9mg *cyclo*(L-Asp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl), methyl ester in 1mL 3:1:1 THF:MeOH:H_2O at 0 °C was added 50µL 1M LiOH. After 1h at 0°C, followed by 2 days at RT, the solution was filtered through a reversed-phase plug (0.5 g C-18) with MeOH as eluant, concentrated under reduced pressure, and purified without workup by RP-HPLC using gradient elution (10min ramp from 5:95 MeCN:H_2O to 25:75 MeCN:H_2O, then 60min ramp to 100% MeCN).

EXAMPLE 133



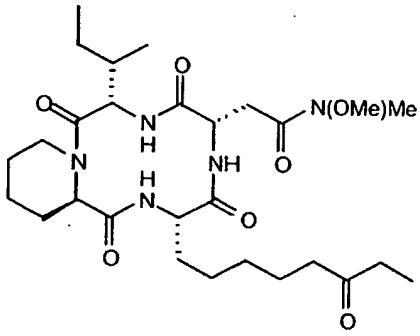
Example 133 was prepared by adding 1mL $Me_3SiCH{=}N_2$ (0.5M solution in hexanes) to 12mg of the carboxylic acid product of Example 132a in 4mL 2:1 MeOH:Et_2O at RT. After 20min, the solution became homogenous and 0.25mL glacial acetic acid was added. The solution was poured into brine, extracted with CH_2Cl_2 and dried with Na_2SO_4. The solution was filtered and concentrated under reduced pressure. Pure Example 133 was obtained following PTLC on silica gel (1 x 1000µm plate) using 1:1 acetone:hexanes as eluant. The methyl ester Example 133 thus obtained was characterized by ^1H NMR and MS [m/z: 537.5 (M^++1)].

EXAMPLE 134



Example 134 was prepared by adding 9.6mg $NaBH_4$ to 120mg of Example 133 in 7mL THF at 0°C. After aging for 3h, the reaction was quenched by the addition of saturated NH_4Cl(aq), extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC using 4:6 acetone:hexanes (Rf = 0.53) as eluant, 117mg of pure Example 134 was obtained which was characterized by ^{1}H NMR.

EXAMPLE 135



Example 135 was prepared by the following methods J and K.

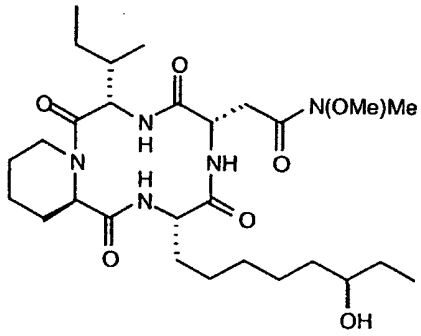
Method J

To 50mg of Example 132a in 2mL CH_2Cl_2 at RT was added sequentially 14μL Et_3N followed by 8μL $MeSO_2Cl$. After aging for 2h, 18mg solid HCl•HN(OMe)Me was added. After an additional hour, the volatiles were removed under reduced pressure. Following flash chromatography on silica gel using 1:2:97 NH_4OH:MeOH:$CHCl_3$ as eluant, 1.9mg pure Example 135 was obtained which was characterized by ^{1}H NMR and MS.

Method K

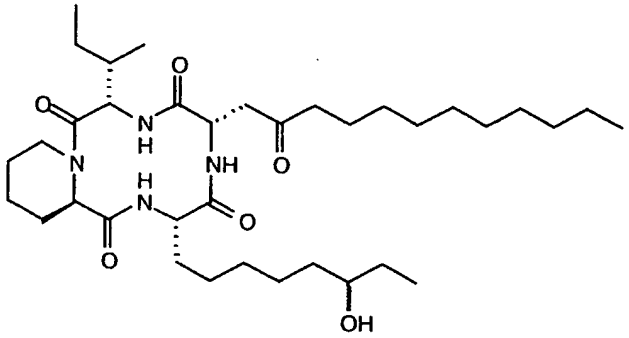
To 20mg of Example 132a in 1mL THF at -78°C was added 10.6mg HCl•HN(OMe)Me followed by the dropwise addition of 112μL *i*PrMgBr (2M solution in THF). The resulting solution was slowly allowed to warm to 4°C and was aged for 12h. The reaction was quenched by addition of 1mL saturated NH_4Cl(aq), extracted with CH_2Cl_2 and dried with Na_2SO_4. Following flash chromatography on silica gel using 1:2:97 NH_4OH:MeOH:$CHCl_3$ as eluant, 11mg pure Example 135 was obtained which was characterized by ^1H NMR and MS.

EXAMPLE 136



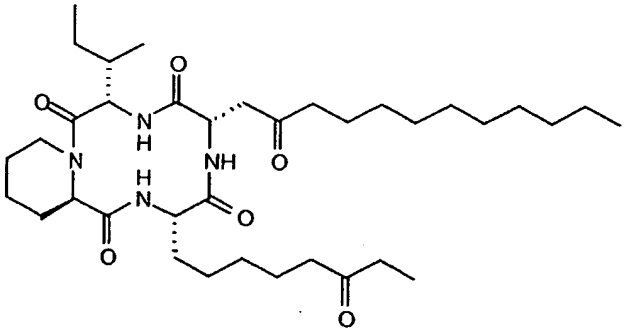
Example 136 was prepared from 117mg of Example 134 using Method K as described in Example 135. This resulted in 76mg of Example 136 (R_f = 0.46, 1:9:90 NH_4OH:MeOH:$CHCl_3$) which was characterized by ^1H NMR and MS [m/z: 568 (M+1)].

EXAMPLE 137



Example 137 was prepared by the following procedure. To 11mg *cyclo*(N-O-methyl-N-methyl-L-Asp-L-Ile-D-Pip-L-2-amino-8-hydroxy-decanoyl) in 0.39mL THF and 80μL HMPA at 0°C was added 388 μL *n*-$C_{10}H_{21}MgBr$ (1M in Et_2O). The solution was warmed immediately to RT and aged for 12h. The solution was poured into saturated NH_4Cl(aq), partitioned with THF and dried with Na_2SO_4. Following PTLC (1 x 500μm plate) on silica gel using 1:9:90 NH_4OH:MeOH:$CHCl_3$ as eluant, 2.5mg pure Example 137 was obtained which was characterized by ^1H NMR and MS [m/z: 649 (M^++1)].

EXAMPLE 138



Example 138 was prepared by adding 5μL pyridine to 2mg of Example 137 in 0.35mL CH_2Cl_2 at 23°C, followed by the addition of 7mg Dess-Martin periodinane. After 1.5h, the solution was poured into 1:1 saturated $NaHCO_3$:10% $NaHSO_3$, aged for 10min, then extracted with CH_2Cl_2, and dried with Na_2SO_4. Following PTLC (1 x 250μm plate) on silica gel using 1:3:96 NH_4OH:MeOH:$CHCl_3$

as eluant, 1.5mg pure Example 138 was obtained which was characterized by ^1H NMR and MS [m/z: 647 (M^++1)].

EXAMPLES 139A-139J

Following the general procedures described in Examples 137 and 138, and utilizing the appropriate starting compounds and reactants - particularly the appropriate nucleophile for the R_1 group - which would be clear to one in the art, the following compounds were prepared:

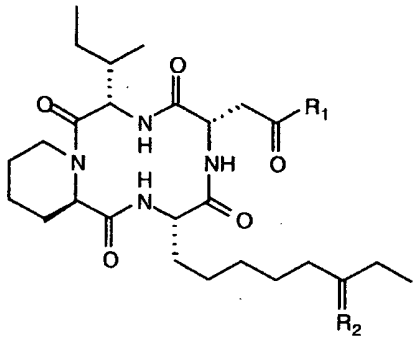
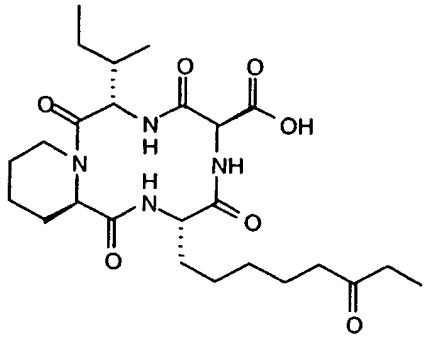


Table 7

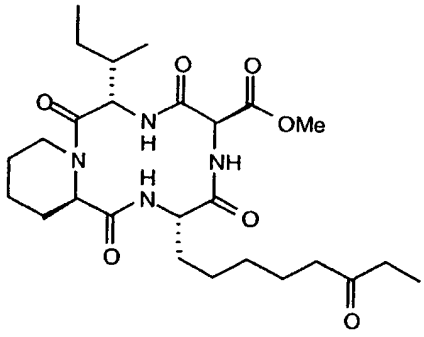
Example	R_1 Group	R_2 Group	Mass Spec
139a	CH_2Ph	H, OH	599 (M^++1)
139b	CH_2Ph	=O	597 (M^++1)
139c	1-napthyl	H, OH	635 (M^++1)
139d	1-napthyl	=O	633 (M^++1)
139g	5-(N-methyl-indolyl)	H, OH	638 (M^++1)
139h	5-(N-methyl-indolyl)	=O	636 (M^++1)
139i	*t*Bu	H, OH	565 (M^++1)
139j	*t*Bu	=O	563 (M^++1)

EXAMPLE 140



Example 140 was prepared by the following procedure. To 100mg *cyclo*(beta-oxo-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) at RT in 6mL 1:1:1 MeCN:CCl_4:H_2O was added 0.7mg $RuCl_3 \cdot 2H_2O$ followed by the addition of 634mg $NaIO_4$ (as a sonicated solution in 2mL H_2O). After 30h, the resulting tan-white heterogeneous solution was partitioned between 1:1 brine:saturated NH_4Cl and 3:7 *i*PrOH:$CHCl_3$. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure to yield 100mg of Example 140. The crude product was characterized by ^1H NMR and MS [m/z: 526 (M^++NH_4)] with no additional purification.

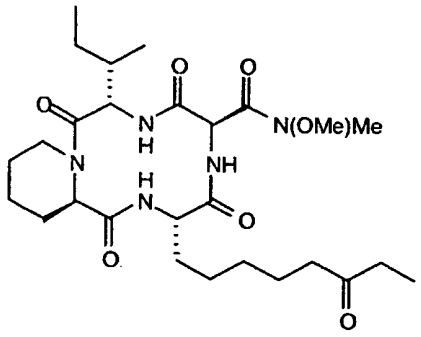
EXAMPLE 141



Example 141 was prepared by the following procedure. To 80mg *cyclo*(D-2-amino-2-carboxy-ethanoyl-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 3.3mL 2:1 MeOH:Et_2O at RT was added 1mL $TMSCHN_2$ (2M in hexanes). After 1.5h, glacial HOAc was added dropwise until foaming ceased and the solution was partitioned between 1:1 brine:saturated NH_4Cl and CH_2Cl_2. The organic layer was

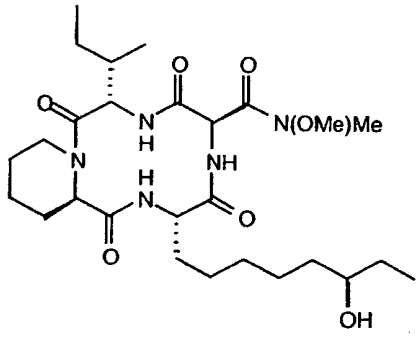
dried with Na_2SO_4. Following PTLC (1 x 1500μm plate) on silica gel using 3:97 HOAc:EtOAc as eluant, 28mg pure Example 141 was obtained which was characterized by ^{1}H NMR and MS [m/z: 540 (M^++NH_4)].

EXAMPLE 142



Example 142 was prepared by the following procedure. To 26.5mg of Example 140 in 2mL CH_2Cl_2 at RT was added 51mg HCl•HN(OMe)Me and 13mg DMAP, followed by the addition of 46mg BOP. After aging for 8h at RT, the solution was warmed to 40°C for 12h. Following removal of volatiles, 2mg pure Example 142 was obtained following PTLC on silica gel using 1:1 acetone:hexanes as eluant. The product was characterized by ^{1}H NMR and MS [m/z: 552 (M^++1)].

EXAMPLE 143



Example 143 was prepared by starting with Example 141. First, the side chain carbonyl of Example 141 was reduced as described in Example 134. The resulting intermediate compound was then treated by the procedure described in Example 135. The pure Example 143 thus obtained was characterized by ^{1}H NMR.

EXAMPLES 144A-144G

Following the general procedures described above in Examples 142 and 143 (procedure of Example 142 was utilized for Example 144g, while the procedure of Example 143 was utilized for the other Examples 144a-144f), and using the appropriate materials which would be clear to one in the art, the following compounds were prepared:

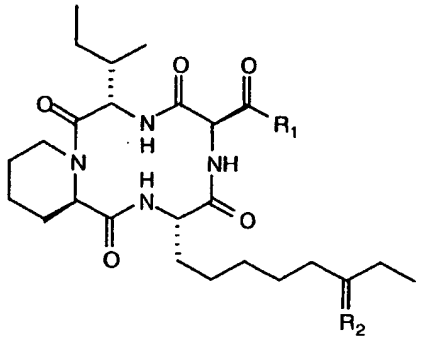
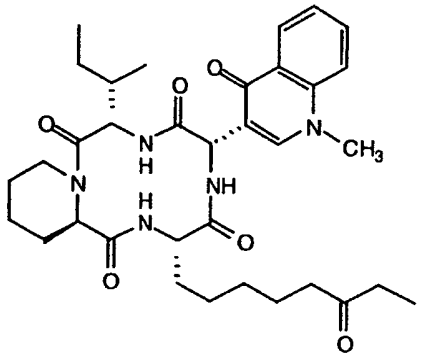


Table 8

Example	R_1 Group	R_2 Group	Mass Spec
144a	CH_2Ph	H, OH	602 (M^++NH_4)
144b	CH_2Ph	=O	600 (M^++NH_4)
144c	*i*Pr	H, OH	537 (M^++1)
144d	*i*Pr	=O	552 (M^++NH_4)
144e	5-(N-methylindolyl)	H, OH	624 (M^++1)
144f	5-(N-methylindolyl)	=O	622 (M^++1)
144g	CH_2Ph	$PhCH_2$–, OH	689 (M^++1)

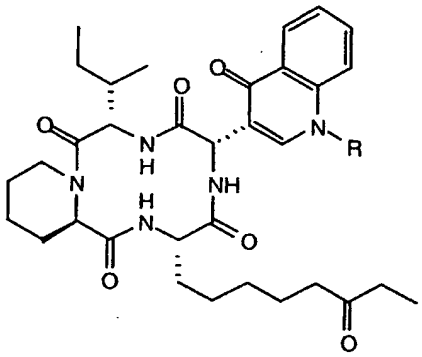
EXAMPLE 145



Example 145 was prepared by the following procedure. To 10mg N-desmethoxy-N-methyl apicidin in 2.5mL CH_2Cl_2 at -78°C was bubbled O_3 until the solution turned light blue. The resulting solution was stirred for 10min and then N_2 was bubbled through the solution for 5min. Next, 250μL Dimethylsulfide was added, the solution then warmed slowly to RT and concentrated under reduced pressure. The resulting residue was dissolved in 1:1 THF:*t*BuOH at 0°C, followed by the addition of 3.7mg *t*BuOK. After 2h at 0°C, the solution was poured into 1:1 water:saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following preparative TLC on silica gel (1 x 500μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, pure Example 145 was obtained which was characterized by ^1H NMR and MS [m/z: 622.7 (M^++1)]. TLC: R_f = 0.15 (1:3:96 NH_4OH:MeOH:$CHCl_3$).

EXAMPLES 146A-146F

Following the general ozonalysis procedure described for Example 145, the following compounds were prepared:

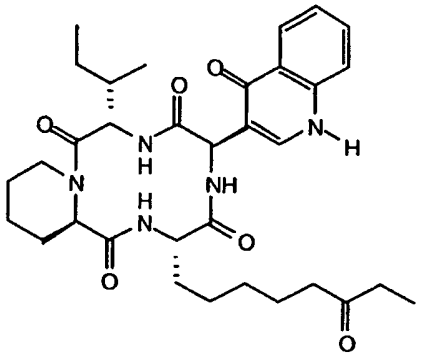


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Table 9

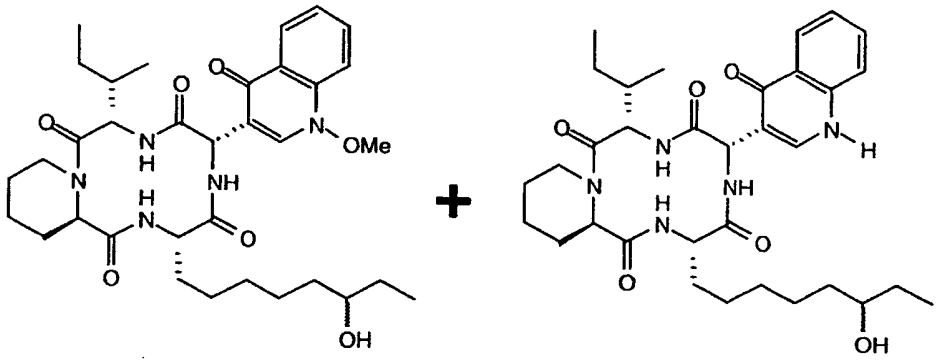
Example	R Group	Starting Compound	Mass Spec
145	Me	Ex. 69	622.7 (M^++1)
146a	H	Apicidin	608.3 (M^++1)
146b	OMe	Apicidin	638.3 (M^++1)
146c	Et	Ex. 74a	636.8 (M^++1)
146d	*n*Pr	Ex. 74b	650.3 (M^++1)
146e	CH_2CO_2Me	Ex. 70	680.7 (M^++1)
146f	CH_2CO_2H	Ex. 79	666.6 (M^++1)

EXAMPLE 147



Example 147 was prepared by the following procedure. To 10mg *cyclo*(L-2-amino-2-(3'-(quinol-4'-onyl))-ethanoyl-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 1mL $ClCH_2CH_2Cl$ at RT was added 4mg DMAP and 19μL TEA, followed by the addition of 5μL $MeSO_2Cl$. After 15min at RT, the solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following preparative TLC on silica gel (1 x 500μm plate) using 1:1 acetone:hexanes as eluant, pure Example 147 was obtained which was characterized by ^1H NMR and MS [m/z: 608.5 (M^++1)]. TLC: R_f = 0.43 (1:1 acetone:hexanes).

EXAMPLES148A AND 148B



Ex. 148a **Ex. 148b**

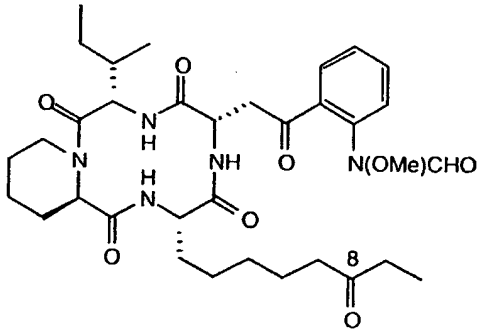
Examples 148a and 148b were prepared by adding 3mg $NaBH_4$ to 20mg *cyclo*(L-2-amino-2-(3'-(N-O-methyl-quinol-4'-onyl))-ethanoyl-L-Ile-D-Pip-L-

2-amino-8-oxo-decanoyl) in 5mL MeOH at 0°C. Then the cooling bath was removed promptly. After 20min, acetone was added to quench the reaction and the solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 and dried with Na_2SO_4. Initial purification was accomplished following flash chromatography on silica gel using 1:1 acetone:hexanes as eluant. At this juncture, it was noted that the resulting product was approximately 1:1 mixture of two compounds with similar TLC R_f values (product A: 0.39 and Product B: 0.28 in 1:1 acetone:hexanes). Repurification by preparative TLC on silica gel (1 x 500μm plate) yielded two pure products which were characterized by ^1H NMR and MS [m/z: 640.6 (M^++1) for Example 148a and 610.5 (M^++1) for Example 148b].

Example 148a: *cyclo*(L-2-amino-2-(3'-(N-O-methyl-quinol-4'-onyl))-ethanoyl-L-Ile-D-Pip-L-2-amino-8-hydroxy-decanoyl); TLC: R_f = 0.55 (1:3:96 NH_4OH:MeOH:$CHCl_3$); HPLC: t_R = 7.17min (1:1 MeCN:H_2O, 1.0mL/min, Zorbax™ RX-8).

Example 148b: *cyclo*(L-2-amino-2-(3'-quinol-4'-onyl)-ethanoyl-L-Ile-D-Pip-L-2-amino-8-hydroxy-decanoyl); TLC: R_f = 0.18 (1:3:96 NH_4OH:MeOH:$CHCl_3$); HPLC: t_R = 5.86min (1:1 MeCN:H_2O, 1.0mL/min, Zorbax™ RX-8).

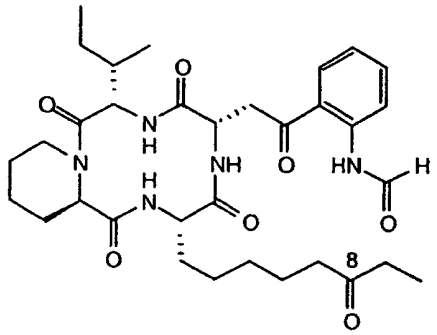
EXAMPLE 149



Example 149 was prepared by the following procedure. Ozone was bubbled through 25mg apicidin in 2.5mL CH_2Cl_2 at -78°C until the resulting solution remained pale blue. After 10min, the solution was purged with a vigorous stream of nitrogen, followed by the addition of 1mL Me_2S. Then the solution was warmed to RT. The volatiles were removed under reduced pressure and pure Example 149 was obtained following PTLC on silica gel (1 x 2000μm plate) using 1:2 acetone:hexanes

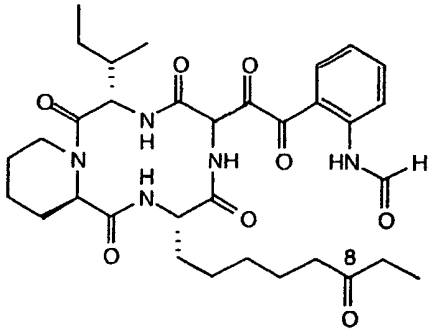
as eluant. The pure Example 149 thus obtained was characterized by ^{1}H NMR and MS [m/z: 662.5 (M^++Li)].

EXAMPLE 150



Example 150 was prepared by the following procedure. Ozone was bubbled through a solution of 470mg N-desmethoxy-apicidin in 40mL CH_2Cl_2 at -78°C for about 10min until a blue color persisted. Then the solution was purged with a vigorous stream on nitrogen, followed by the addition of 1mL Dimethylsulfide. The resulting solution was allowed to warm to RT and the volatiles were removed under reduced pressure. Following flash chromatography on silica gel using gradient elution (2:3 to 1:1 acetone:hexanes), 320mg pure Example 150 was obtained which was characterized by ^{1}H NMR and MS [m/z: 626 (M^++1)].

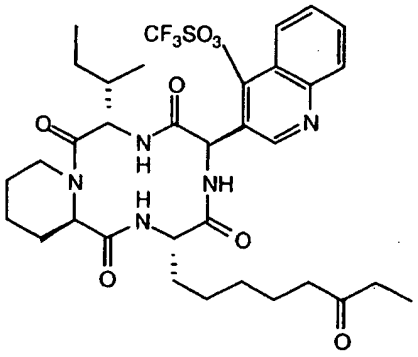
EXAMPLE 151



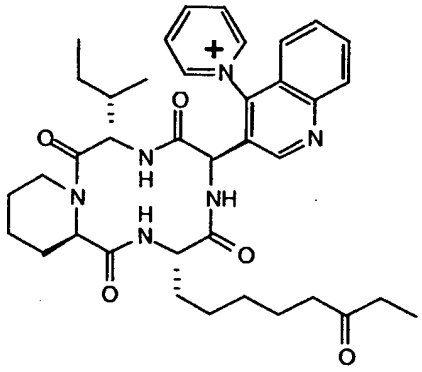
Example 151 was prepared similarly to the procedure described for Example 150 utilizing beta-oxo-N-desmethoxy-apicidin as the starting material.

Example 151 thus obtained was characterized by ^{1}H NMR and MS [m/z: 640 (M^++1)].

EXAMPLES 152A AND 152B



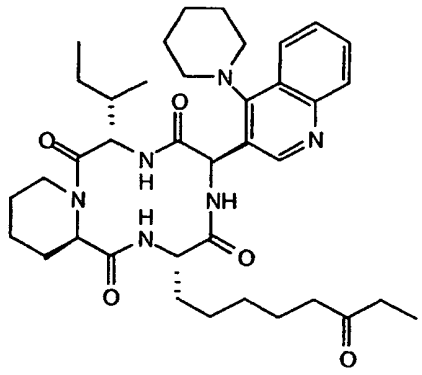
Ex. 152a



Ex. 152b

Examples 152a and 152b were prepared by adding 30μL pyridine to 43mg *cyclo*(L-2-amino-2-(3'-quinol-4'-onyl)-ethanoyl-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 1.2mL CH_2Cl_2. The mixture was cooled to 0 °C. To the resulting solution was added 14μL $(CF_3SO_2)_2O$. After 40min, the solvent was removed *in vacuo*. The crude pyridinium salt thus obtained was characterized by ^{1}H NMR and MS [m/z: 740 (M^++1)].

EXAMPLE 153



Example 153 was prepared by the following methods L and M.

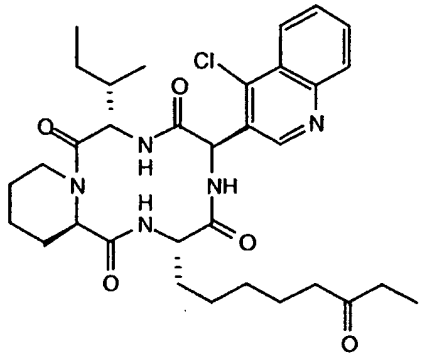
Method L

To 52mg crude *cyclo*(L-2-amino-2-(3'-(4'-pyridium-quinolyl))-ethanoyl-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 4mL CH_2Cl_2 at RT was added 1mg 20% $Pd(OH)_2$ Degussa catalyst. A hydrogen atmosphere (balloon pressure) was established. After 12h, the catalyst was removed by filtration through Celite using acetone as eluant. Following PTLC (1 x 1000 μm plate) on silica gel using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, 28mg pure Example 153 was obtained which was characterized by ^1H NMR and MS [m/z: 675 (M^++1)].

Method M

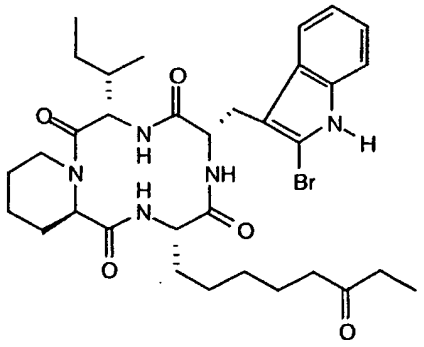
To 20mg *cyclo*(L-2-amino-2-(3'-quinol-4'-onyl)-ethanoyl-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 0.6mL CH_2Cl_2 at 0 °C was added 8mg 2,6-di-t-butyl-4-methyl-pyridine followed by 7μL $(CF_3SO_2)_2O$. After 3.5h, 7μL piperidine was added, the solution was aged for 2.5h and then was warmed to RT for 12h. Following PTLC without workup (1 x 500μm plate) on silica gel using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, 6mg pure Example 153 was obtained which was characterized by ^1H NMR and MS [m/z: 675 (M^++1)].

EXAMPLE 154



Example 154 was prepared by the following procedure. At 23°C, 13mg of Example 146a was placed in 360μL DMF. Then 5.3mg 2,6-di-*tert*-butyl-4-methyl-pyridine was added followed by 6.9mg 2,4-dinitrobenzenesulfonyl chloride. After aging for 6h, 2.7mg LiCl was added and the solution was warmed to 60°C for 12h. The reaction was cooled to RT, quenched by the addition of water, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC on silica gel (1 x 500μm plate) using 1:9:90 NH_4OH:MeOH:$CHCl_3$ as eluant, 5mg pure Example 154 was obtained which was characterized by ^1H NMR and MS [m/z: 626 (M^++1)].

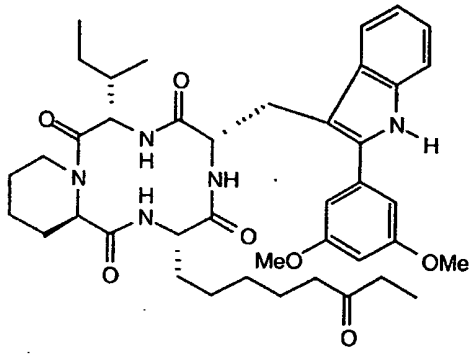
EXAMPLE 155



Example 155 was prepared by mixing 1.2g N-Desmethoxy-apicidin, 360mg N-bromosuccinamide and 15mg benzoyl peroxide in 70mL CCl_4. The resulting mixture was heated to 80°C for 15min. The solvent was then removed under reduced pressure and the crude product was purified in two batches by RP-HPLC

using 4:6 MeCN:H_2O as eluant to yield 400mg pure Example 155 which was characterized by ^1H NMR and MS [m/z: 674 (M^++1)].

EXAMPLE 156



Example 156 was prepared by dissolving 100mg *cyclo*(2-bromo-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxo-decanoyl) in 3mL dioxane and 3mL EtOH. Then 63mg LiCl, 270mg (3,5-diMeO)PhB(OH)$_2$ and 1.5mL 1M $NaHCO_3$ was added. To the resulting mixture was added 17mg $Pd(PPh_3)_4$ and the resulting solution was heated in sequence to 90°C for 90min, 100°C for 15min and 80°C for 12h. The solution was poured into 1:1 saturated $NaHCO_3$:brine, extracted with CH_2Cl_2 and dried with Na_2SO_4. Following preparative TLC on silica gel (1 x 500μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant (four developments), 67 pure Example 156 was obtained which was characterized by ^1H NMR and MS [m/z: 730 (M^++1)].

EXAMPLES 157A-157D

Examples 157a-157d were prepared following the procedure described in Example 156.

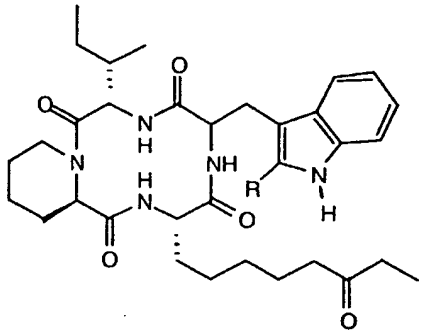
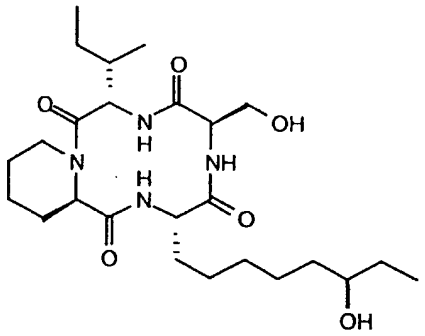


Table 10

Example	R Group	Mass Spec
156	Ph(3,5-OMe)	730 (M^++1)
157a	2-napthyl	720 (M^++1)
157b	5-(N-methylindolyl)	723 (M^++1)
157c	1-napthyl	720 (M^++1)
157d	Ph	687 (M^++NH_4)

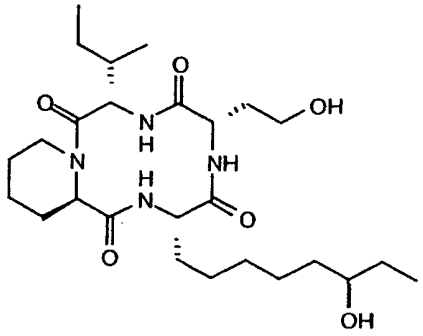
EXAMPLE 158



Example 158 was prepared by adding 9mg $NaBH_4$ to 100mg of Example 141 in 6mL THF at 0°C. After 2h, the reaction was quenched by the

addition of acetone followed by the addition of saturated $NaHCO_3$(aq), extracted with CH_2Cl_2 and dried with Na_2SO_4. This yielded 10mg pure diol Example 158 (R_f= 0.37) following PTLC on silica gel using 3:7 acetone:hexanes as eluant. The product thus obtained was characterized by ^1H NMR.

EXAMPLE 159



Example 159 was prepared by the following methods N and O.

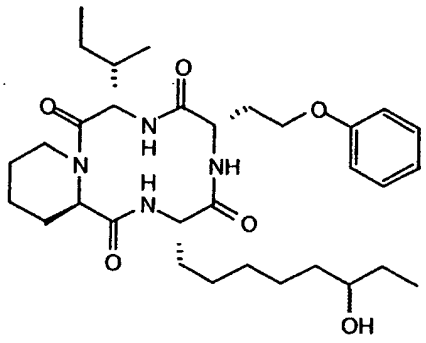
Method N:

To 100mg of Example 133 in 3.5mL THF at 0°C was added 11.6mg $LiBH_4$. After aging for 4h at 0°C, the reaction was warmed to RT. After an additional 2h, the reaction was quenched by the addition of acetone followed by the addition of saturated brine(aq), extracted with 3:7 *i*PrOH:$CHCl_3$ and dried with Na_2SO_4. Following PTLC on silica gel using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, 60mg pure diol Example 159 was obtained which was characterized by ^1H NMR and MS [m/z: 511 (M^++1)].

Method O

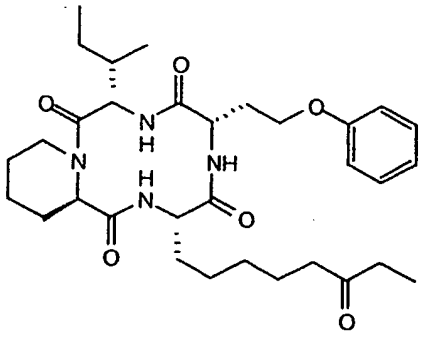
To 250mg of Example 133 in 11mL THF at 0°C was added 2.65mL DIBAL-H (1M solution in toluene). After aging for 4h at 0°C, the reaction was quenched by the addition of acetone followed by the addition of saturated brine, extracted with 3:7 *i*PrOH:$CHCl_3$ and dried with Na_2SO_4. Following flash chromatography on silica gel using 1:3:96 to 1:9:90 NH_4OH:MeOH:$CHCl_3$ gradient elution, 100mg pure diol Example 159 (R_f= 0.41, 1:9:90 NH_4OH:MeOH:$CHCl_3$) was obtained which was characterized by ^1H NMR.

EXAMPLE 160



Example 160 was prepared by the following procedure. To 27mg Ph_3Bi dissolved in 1mL CH_2Cl_2 at RT was added 0.5μL CH_3CO_3H. After 10min, a Ph_3Bi/CH_3CO_3H solution resulted. To the solution, 22mg of Example 159 was added as a solution in 1mL CH_2Cl_2, followed by the addition of 3.5mg $Cu(OAc)_2$. The resulting solution was then warmed to 60°C for 3h. After cooling to RT, the reaction was quenched by the addition of saturated $NaHCO_3$(aq), extracted with 3:7 *i*PrOH:$CHCl_3$ and dried with Na_2SO_4. Following PTLC on silica gel using 4:6 acetone:hexanes (R_f = 0.66) as eluant, 4mg pure Example 160 was obtained which was characterized by ^{1}H NMR and MS [m/z: 587 (M^++1)].

EXAMPLE 161



Example 161 was prepared by oxidizing 3mg of Example 160 using Dess-Martin reagent similarly to the general procedure described in Example 138. This resulted in 2mg Example 161, which was characterized by ^{1}H NMR and MS [m/z: 585 (M^++1)].

EXAMPLES 162A AND 162B

Following the general procedure for Examples 160 and 161, the following Examples 162a and 162b were prepared and characterized by NMR and MS:

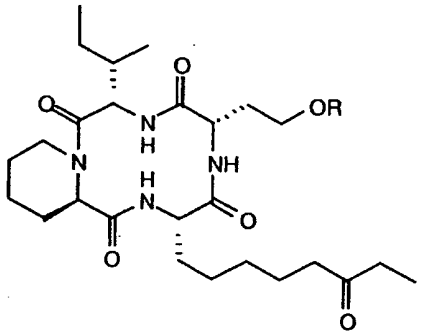
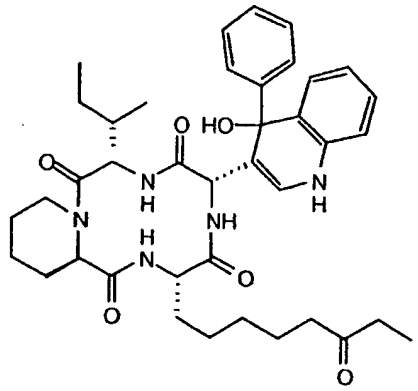


Table 12

Example	R Group	Mass Spec
161	Ph	585 (M+1)
162a	Ph(4-OPh)	-----
162b	Ph(4-F)	-----

EXAMPLE 163



Example 163 was prepared by the following procedure. To 68mg of Example 148a in 6mL THF at RT was added 2mL PhMgBr (2M solution in THF). After aging at RT for 20h, the reaction was quenched by the addition of saturated NH_4Cl(aq), extracted with CH_2Cl_2 and dried with Na_2SO_4. Following PTLC on silica gel (1 x 1500μm plate) using 1:9:90 NH_4OH:MeOH:$CHCl_3$ as eluant, 18.9 mg pure intermediate compound having a side chain alcohol (R_f= 0.49, 1:9:90 NH_4OH:MeOH:$CHCl_3$) was obtained which was characterized by ^{1}H NMR. The side chain alcohol of the intermediate was then oxidized using Dess-Martin reagent as described in Example 138. Following PTLC on silica gel (1 x 500μm plate) using 1:9:90 NH_4OH:MeOH:$CHCl_3$ as eluant, 13mg pure Example 163 was obtained (R_f= 0.66, 1:9:90 NH_4OH:MeOH:$CHCl_3$) which was characterized by ^{1}H NMR and MS [m/z: 684 (M^++1)].

EXAMPLES 164A AND 164B

Following the general procedure for Example 163, the following Examples 164a and 164b were prepared:

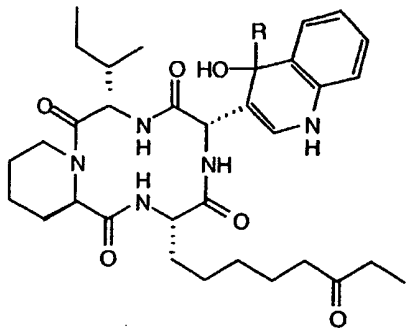
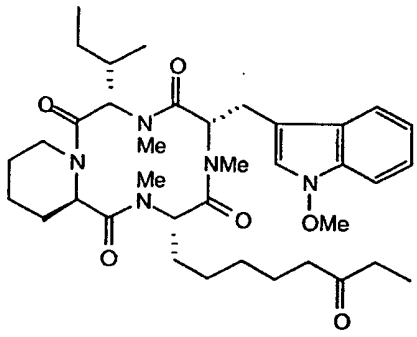


Table 13

Example	R Group	Mass Spec
163	Ph	684 (M^++1)
164a	Ph(4-*t*Bu)	757.8 (M^++NH_4)
164b	CH_2Ph	698 (M^++1)

EXAMPLE 165



Example 165 was prepared by the following procedure. To 20mg apicidin in 321μL DMF at RT was added 16μL MeI followed by the addition of 3.8mg NaH (60% suspension in mineral oil). After 20h, water was added and the solution extracted with EtOAc and dried with Na_2SO_4. Following PTLC on silica gel (1 x 1000μm plate) using 1:3:96 NH_4OH:MeOH:$CHCl_3$ as eluant, 9.9mg pure

Example 165 was obtained which was characterized by ^{1}H NMR and MS [m/z: 666 (M^++1)].

EXAMPLES 166A-166C

Examples 166a-166c were prepared similarly to the procedure described in Example 165. Apicidin was treated with benzyl bromide, in place of the methyl iodide in Example 165, to yield a mixture of mono-, di- and tri-benzylated derivatives. The three compounds, Examples 166a-166c, thus obtained were characterized by ^{1}H NMR and MS. The regiochemistry of the mono- and di-benzylated derivatives was not established.

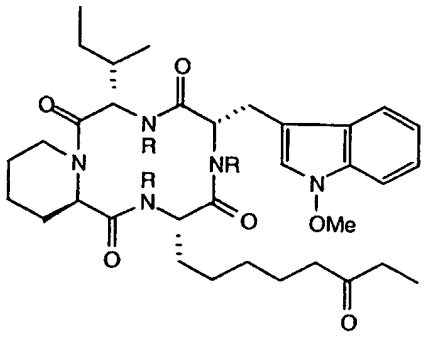
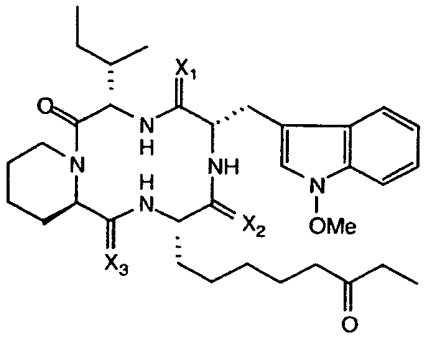


Table 14

Example	R Groups	Mass Spec
166a	Mono-benzylated	714 (M^++1)
166b	Di-benzylated	804 (M^++1)
166c	Tri-benzylated	894 (M^++1)

EXAMPLES 167A-167D



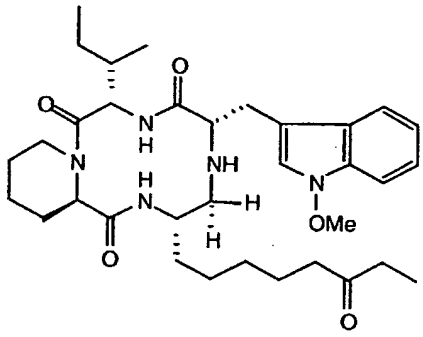
Examples 167a-167d were prepared by the following procedure. To 10mg apicidin in 2mL toluene was added 13mg Lawesson's reagent. The resulting solution was heated at 80°C for 25min and then cooled to RT. The entire solution was loaded directly onto a silica gel flash chromatography column and purified by gradient elution (100 % $CHCl_3$, one column, followed by 1:3:96 NH_4OH:MeOH:$CHCl_3$ elution) to yield two fractions: monothiono Example 167a (Fraction One - Product A, Rf = 0.83, 1:3:96 NH_4OH:MeOH:$CHCl_3$) and impure bis- and tris-thiono Examples 167b-167d (Fraction Two – Products B, C, and D, Rf = 0.68, 1:3:96 NH_4OH:MeOH:$CHCl_3$). Fraction Two was further purified by preparative RP-HPLC using gradient elution (2:3 MeCN:H_2O to 100% MeCN, 70min linear gradient). The products thus obtained were characterized by ^1H NMR and MS. The following retention times were obtained for the four products during the preparative RP-HPLC run:

t_R = 34.2min (product A – Example 167a); 39.9min (product B – Example 167b); 45.6min (product C – Example 167c); 48.8min (product D – Example 167d); (2:3 MeCN:H_2O to 100% MeCN, 70min linear gradient).

Table 15

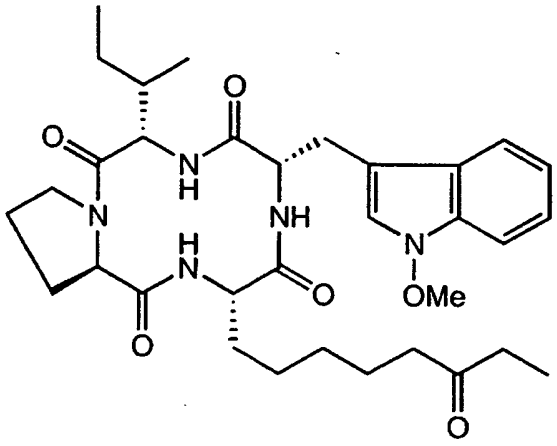
Example	Product	X_1	X_2	X_3	Mass Spec
167a	Product A	S	O	O	640.3 (M^++1)
167b	Product B	S	S	O	656.3 (M^++1)
167c	Product C	S	O	S	656.3 (M^++1)
167d	Product D	S	S	S	672.3 (M^++1)

EXAMPLE 168

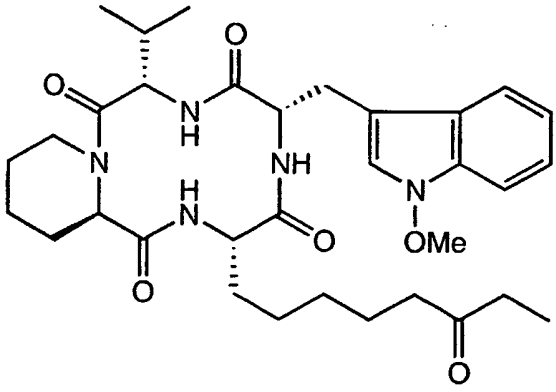


Example 168 was prepared by adding 0.160mL BH3•THF (1M solution in THF) to 10mg apicidin in 2mL THF at 0°C. After 30min, the resulting solution was warmed to RT and aged for 12h. At this point, after 12.5h total, the solution was heated to 60°C for 30min, then cooled to RT. Then, 1mL methanol was added, followed by the addition of 0.15mL $Me_2NCH_2CH_2OH$, and the solution was stirred for 2h. The stirred solution was poured into saturated brine, extracted with EtOAc, and dried with Na_2SO_4. The volatiles were removed under reduced pressure and the crude product was filtered through a 1.5inch pad of silica gel using 1:3:96 $NH_4OH/MeOH/CHCl_3$ as eluant to remove baseline contaminants. The filtered solution was concentrated under reduced pressure and pure product was obtained following preparative RP-HPLC using 1/3 $MeCN/H_2O$ isocratic for 20 min, followed by a 60min linear gradient to 100% MeCN. The pure Example 168 thus obtained was characterized by ^1H NMR and MS [m/z: 612.4 (M^++1)]. HPLC: t_R = 6.69min, 1/1 $MeCN:H_2O$, 1.5mL/min, Zorbax™ RX-8 column. TLC: R_f = 0.50, 1:3:96 $NH_4OH:MeOH:CHCl_3$.

EXAMPLES 169 AND 170



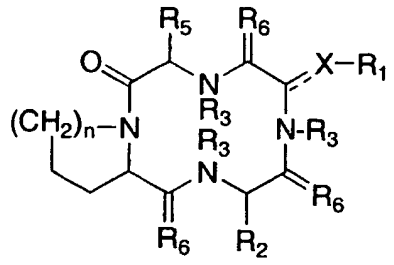
Ex. 169



Ex. 170

WHAT IS CLAIMED IS:

1. A compound having a Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

X is	(1)	$-CH_2-$,
	(2)	$-C(O)-$,
	(3)	$-CH(OR^a)-$,
	(4)	$=CH-$, or
	(5)	not present;
n is	(1)	one, or
	(2)	two;
R_1 is	(1)	R_7,
	(2)	$C(O)R_7$,
	(3)	CN,
	(4)	CO_2R^b,
	(5)	$C(O)N(OR^b)R^c$,
	(6)	$C(O)NR^cR^d$,
	(7)	$NHCO_2R^b$,
	(8)	$NHC(O)NR^cR^d$,
	(9)	$(C_0\text{-}C_4alkyl)OR^a$,
	(10)	$(C_0\text{-}C_4alkyl)OCO_2R^b$,
	(11)	$(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,
	(12)	$C(O)NR^cNR^cR^d$,
	(13)	$C(O)NR^cSO_2R^b$,

(14) $OS(O)_{ni}R_7$,

(19) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,

(20) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, (C_0-C_6alkyl)aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(21) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(22) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is

oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent;

R_2 is
(1) optionally substituted C_2-C_{12}alkyl,
(2) optionally substituted C_2-C_{12}alkenyl,
(3) optionally substituted C_2-C_{12}alkynyl, or
(4) $(CH_2)_{nii}$-O-$(CH_2)_{mii}$ wherein nii, mii = 0 to 7,

wherein the optional substituents on the C_2-C_{12}alkyl, C_2-C_{12}alkenyl, and C_2-C_{12}alkynyl are 1 to 8 groups and each group independently is

(a) CO_2R^a,
(b) $C(O)R^b$,
(c) $C(O)N(OR^b)R^c$,
(d) $C(O)NR^cR^d$,
(e) $C(O)NR^cNR^cR^d$,
(f) $C(O)NR^cSO_2R_7$,
(g) C_3-C_8cycloalkyl,
(h) C_2-C_5alkenyl,
(i) cyano,
(j) $=NOR^a$,
(k) $=NNR^bR^c$,
(l) $=NNR^bS(O)_{ni}R_7$,
(m) $N(OR^b)C(O)NR^bR^c$,
(n) $N(OR^b)C(O)R_7$,
(o) $NHC(O)N(OR^b)R^c$,
(p) $NR^cCO_2R^b$,
(q) $NR^cC(O)NR^cR^d$,
(r) $NR^cC(S)NR^cR^d$,
(s) $NR^cC(O)R_7$,
(t) $NR^bS(O)_{ni}R_7$,
(u) $NR^cCH_2CO_2R^a$,
(v) $NR^cC(S)R_7$,
(x) $NR^cC(O)CH_2OH$,
(y) $NR^cC(O)CH_2SH$,
(z) $NR^cCH_2CO_2R^a$,

(aa) $NR^cCH_2CH(OH)R_7$,
(bb) $NR^cP(O)(OR^a)R_7$,
(cc) NY^1Y^2, wherein Y^1 and Y^2 are independently H or C_1-C_{10}alkyl,
(dd) NO_2,
(ee) $N(OR^b)C(O)R^b$,
(ff) C_1-C_{10}alkanoylamino,
(gg) OR^a,
(hh) $OS(O)_{ni}R_7$,
(ii) oxo,
(jj) OCO_2R^b,
(kk) $OC(O)NR^cR^d$,
(ll) $P(O)(OR^a)_2$,
(mm) $P(O)(OR^a)R_7$,
(nn) $SC(O)R_7$,
(oo) $S(O)_{ni}R_7$,
(pp) SR_7,
(qq) $S(O)_{ni}NR^cR^d$,
(rr) $NR^cCH_2CO_2R^a$,
(ss) diazo,
(tt) C_1-C_5 perfluoroalkyl,
(uu) $B(O)(OR^a)OR^a$,
(xx) halogen,
(yy) aryl(C_0-C_5alkyl), wherein the aryl is optionally substituted with 1 to 3 groups, wherein each group independently is R^f, or
(xx) a 3- to 8-membered heterocycle containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is R^f, and the heterocycle may be saturated or partly unsaturated;

R_3 each independently is

(1) hydrogen,
(2) halogen,

(3) OR^a,
(4) C_1-C_4alkyl, or
(5) C_1-C_4aryl;

R_5 is (1) isopropyl, or
(2) sec-butyl;

R_6 each independently is
(1) O,
(2) S, or
(3) H;

R_7 is (1) hydrogen,
(2) optionally substituted C_2-C_{10}alkyl,
(3) optionally substituted C_2-C_{10}alkenyl,
(4) optionally substituted C_2-C_{10}alkynyl,
(5) optionally substituted C_3-C_8cycloalkyl,
(6) optionally substituted C_5-C_8cycloalkenyl,
(7) optionally substituted aryl,

wherein the optional substituents on the C_2-C_{10}alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_8cycloalkyl, C_5-C_8cycloalkenyl and aryl are 1 to 4 groups, and each group independently is
(a) C_1-C_5alkyl,
(b) X^1-C_1-C_{10}alkyl, wherein X^1 is O or $S(O)_{ni}$,
(c) C_3-C_8cycloalkyl,
(d) hydroxy,
(e) halogen,
(f) cyano,
(g) carboxy,
(h) NY^1Y^2, wherein Y^1 and Y^2 are independently H or C_1-C_{10}alkyl,
(i) nitro,
(j) C_1-C_{10}alkanoylamino,
(k) aroyl amino wherein the aroyl is optionally substituted with 1 to 3 groups wherein each group independently is R^{f1}, wherein R^{f1} is defined by any of the definitions below for R^f except for (14), (26), (27), and (32),

(l) oxo,

(m) aryl C_0-C_5alkyl wherein the aryl is optionally substituted with 1 to 3 groups, wherein each group independently is R^{f1},

(q) C_1-C_5perfluoroalkyl,

(r) $N(OR^b)C(O)R_7'$, wherein R_7' is any of the above definitions of R_7 from (1) to (7)(n), and below of R_7 from (8) to (12), or

(s) $NR^cC(O)R_7'$,

(8) a 5- to 10-membered heterocycle containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen and the heterocycle is optionally substituted by 1 to 3 groups, each group independently is R^{f1}, and the heterocycle may be saturated or partly unsaturated,

(9) a benzene ring fused to a 5- to 10-membered heterocyclic ring containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen and the heterocycle is optionally substituted by 1 to 3 groups, each group independently is R^{f1}, and the heterocycle may be saturated or partly unsaturated,

(10) a 5- to 10-membered heterocyclic ring containing from 1 to 4 heteroatoms fused to a second 5- to 10-membered heterocyclic ring containing from 1 to 4 heteroatoms, each heteroatom in either heterocyclic ring independently is oxygen, sulfur or nitrogen and the second heterocyclic ring is optionally substituted by 1 to 3 groups, each group independently is R^{f1}, and each heterocycle independently may be saturated or partly unsaturated,

(11) a benzene ring fused to a C_3-C_8cycloalkyl ring, wherein the cycloalkyl is optionally substituted by 1 to 3 groups each independently being R^{f1}, and the cycloalkyl ring may be saturated or partly unsaturated, or

(12) a 5- to 10-membered heterocyclic ring containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen, the heterocyclic ring is fused to a C_3-C_8cycloalkyl ring, wherein the cycloalkyl ring is optionally substituted by 1 to 3 groups

each independently being R^{f1}, and the cycloalkyl ring may be saturated or partly unsaturated,

R^a is (1) hydrogen,

(2) optionally substituted C_1-C_{10}alkyl,

(3) optionally substituted C_3-C_{10}alkenyl,

(4) optionally substituted C_3-C_{10}alkynyl,

(5) optionally substituted C_1-C_{10}alkanoyl,

(6) optionally substituted C_3-C_{10}alkenoyl,

(7) optionally substituted C_3-C_{10}alkynoyl,

(8) optionally substituted aroyl,

(9) optionally substituted aryl,

(10) optionally substituted C_3-C_7cycloalkanoyl,

(11) optionally substituted C_5-C_7cycloalkenoyl,

(12) optionally substituted C_1-C_{10}alkylsulfonyl,

(13) optionally substituted C_3-C_8cycloalkyl,

(14) optionally substituted C_5-C_8cycloalkenyl,

wherein the optional substituents on the C_1-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_1-C_{10}alkanoyl, C_3-C_{10}alkenoyl, C_3-C_{10}alkynoyl, aroyl, aryl, C_3-C_7cycloalkanoyl, C_5-C_8cycloalkenyl, C_1-C_{10}alkylsulfonyl, C_3-C_8cycloalkyl and C_5-C_8cycloalkenyl are from 1 to 10 groups, wherein each group independently is hydroxy, C_1-C_6alkoxy, C_3-C_7cycloalkyl, aryl C_1-C_3alkoxy, NR^xR^x, CO_2R^b, $CONR^cR^d$, or halogen,

(15) C_1-C_5perfluoroalkyl,

(16) arylsulfonyl optionally substituted with 1 to 3 groups, wherein each group independently is C_1-C_5alkyl, C_1-C_5perfluoroalkyl, nitro, halogen or cyano,

(17) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, wherein each heteroatom is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 4 groups, wherein each group independently is C_1-C_5alkyl, C_1-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, and wherein the heterocycle may be saturated or partly unsaturated, or

(18) $OP(O)(OR^b)_2$;

R^b is (1) H,

(2) optionally substituted aryl,

(3) optionally substituted C_1-C_{10}alkyl,

(4) optionally substituted C_3-C_{10}alkenyl,

(5) optionally substituted C_3-C_{10}alkynyl,

(6) optionally substituted C_3-C_{15}cycloalkyl,

(7) optionally substituted C_5-C_{10}cycloalkenyl, or

(8) optionally substituted 5- to 10-membered heterocycle containing 1 to 4 heteroatoms, wherein each heteroatom independently is oxygen, sulfur, or nitrogen,

wherein the optional substituents on the aryl, C_1-C_{10}alkyl, C_3-C_{10}alkenyl, C_3-C_{10}alkynyl, C_3-C_{15}cycloalkyl, C_5-C_{10}cycloalkenyl, or 5- to 10-membered heterocycle are from 1 to 10 groups, wherein each group independently is

(a) hydroxy,

(b) C_1-C_6alkyl,

(c) oxo,

(d) $SO_2NR^xR^x$,

(e) aryl C_1-C_6alkoxy,

(f) hydroxy C_1-C_6alkyl,

(g) C_1-C_{12}alkoxy,

(h) hydroxy C_1-C_6alkoxy,

(I) amino C_1-C_6alkoxy,

(j) cyano,

(k) mercapto,

(l) (C_1-C_6alkyl)-$S(O)_{ni}$-(C_0-C_6alkyl),

(m) C_3-C_7cycloalkyl optionally substituted with 1 to 4 groups, wherein each group independently is R^e,

(n) C_5-C_7cycloalkenyl,

(o) halogen,

(p) C_1-C_5alkanoyloxy,

(q) $C(O)NR^xR^x$,

(r) CO_2R^i,

(s) formyl,

(t) $-NR^xR^x$,

(u) 5 to 9-membered heterocycle, which may be saturated or partially unsaturated, containing from 1 to 4 heteroatoms, wherein each heteroatom independently is oxygen, sulfur or nitrogen, and the heterocycle is optionally substituted with 1 to 5 groups, wherein each group independently is R^e,

(vi) optionally substituted aryl, wherein the optional substituents are 1,2-methylenedioxy or 1 to 5 groups, wherein each group independently is R^e,

(x) optionally substituted aryl C_1-C_3alkoxy, wherein the optional substituents are 1,2-methylenedioxy or 1 to 5 groups, wherein each group independently is R^e, or

(y) C_1-C_5perfluoroalkyl;

R^c and R^d are independently selected from R^b; or R^c and R^d together with the N to which they are attached form a 3- to 10-membered ring containing 0 to 2 additional heteroatoms, each additional heteroatom independently being oxygen, nitrogen, or $(O)_{ni}$ substituted sulfur, wherein the ring is optionally substituted with 1 to 3 groups, wherein each group independently is R^g, hydroxy, thioxo, or oxo;

R^e is

(1) halogen,

(2) C_1-C_7alkyl,

(3) C_1-C_3perfluoroalkyl,

(4) $-S(O)_mR^i$,

(5) cyano,

(6) nitro,

(7) $R^iO(CH_2)_v$-,

(8) $R^iCO_2(CH_2)_v$-,

(9) $R^iOCO(CH_2)_v$,

(10) optionally substituted aryl wherein the optional substituents are from 1 to 3 groups, wherein each group independently is halogen, C_1-C_6alkyl, C_1-C_6alkoxy, or hydroxy,

(11) $SO_2NR^xR^x$,

(12) CO_2R^x, or

(13) NR^xR^x;

R^f is (1) C_1-C_4alkyl,

(2) X^1-C_1-C_4alkyl, wherein X^1 is O or $S(O)_{mi}$,

(3) C_2-C_4alkenyl,

(4) C_2-C_4 alkynyl,

(5) C_1-C_3perfluoroalkyl,

(6) NY^3Y^4, wherein Y^3 and Y^4 are each independently hydrogen, C_1-C_5alkyl, or SO_2R^b,

(7) hydroxy,

(8) halogen,

(9) C_1-C_5alkanoyl amino,

(18) (C_0-C_4alkyl)CO_2R^a,

(19) (C_0-C_4alkyl)$C(O)NR^bR^c$,

(20) (C_0-C_4alkyl)NY^5Y^6 wherein Y^5 and Y^6 together with the N to which they are attached form a 3- to 7-membered ring containing 0 to 2 additional heteroatoms, wherein the additional heteroatoms independently are oxygen, nitrogen, or $(O)_{mi}$ substituted sulfur, wherein the ring is optionally substituted with 1 to 3 groups, wherein each group independently is R^e or oxo,

(13) (C_0-C_4alkyl)NO_2,

(14) (C_0-C_4alkyl)$C(O)R_7$,

(15) (C_0-C_4alkyl)CN,

(16) oxo,

(17) (C_0-C_4alkyl)$C(O)N(OR^b)R^c$,

(18) (C_0-C_4alkyl)$C(O)NR^cR^d$,

(19) (C_0-C_4alkyl)$NHC(O)OR^b$,

(20) (C_0-C_4alkyl)$NHC(O)NR^cR^d$,

(21) (C_0-C_4alkyl)OR^a,

(22) (C_0-C_4alkyl)OCO_2R^b,

(23) (C_0-C_4alkyl)$OC(O)NR^cR^d$,

(24) (C_0-C_4alkyl)$C(O)NR^cNR^cR^d$,

(25) (C_0-C_4alkyl)$C(O)NR^cSO_2R^b$,

(26) (C_0-C_4alkyl)$OS(O)_{ni}R_7$,

(27) (C_0-C_4alkyl)$NR^bS(O)_{ni}R_7$,

(28) C_0-C_4alkyl halogen,

(29) (C_0-C_4alkyl) SR^a,

(30) $P(O)(OR^a)_2$,

(33) C_0-C_4alkyl azide,

(34) C_0-C_4aryl substituted with from 1 to 4 groups, wherein each group independently is $S(O)_2R_7$, or

(33) C_0-C_4aryl where the aryl group is optionally substituted from 1 to 4 groups, wherein each group independently is CO_2R^b, $C(O)NR^cR^d$, NO_2, halogen, $OC(O)R^a$, OR^a or C_1-C_4alkyl;

R^g and R^h together with the N to which they are attached form a 3- to 7-membered ring containing 0 to 2 additional heteroatoms, wherein each additional heteroatom independently is oxygen, nitrogen, or $(O)_{mi}$ substituted sulfur, and the ring is optionally substituted with 1 to 3 groups, wherein each group independently is R^e or oxo; or

R^g and R^h are each independently

(1) hydrogen,

(2) C_1-C_6alkyl optionally substituted with hydroxy, amino, or CO_2R^i,

(3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C_1-C_7alkoxy, C_1-C_7alkyl, or C_1-C_3perfluoroalkyl,

(4) aryl C_1-C_6alkyl, wherein the aryl is optionally substituted with C1-C3perfluoroalkyl or 1,2-methylenedioxy,

(5) C_1-C_5alkoxycarbonyl,

(6) C_1-C_5alkanoyl,

(19) C_1-C_5alkanoyl C_1-C_6alkyl,

(20) arylC_1-C_5 alkoxycarbonyl,

(21) aminocarbonyl,

(22) (C_1-C_5monoalkyl)aminocarbonyl,

(23) (C_1-C_5dialkyl)aminocarbonyl, or

(24) CO_2R^b;

R^i is

(1) hydrogen,

(2) C_1-C_3perfluoroalkyl,

(3) C_1-C_6alkyl, or

(4) optionally substituted aryl C_0-C_6alkyl, wherein the aryl optional substituents are from 1 to 3 groups, wherein each group independently is halogen, C_1-C_6alkyl, C_1-C_6alkoxy, or hydroxy;

R^x is a C_1-C_4alkyl;

m is 0 to 2;

mi is 0 to 2;

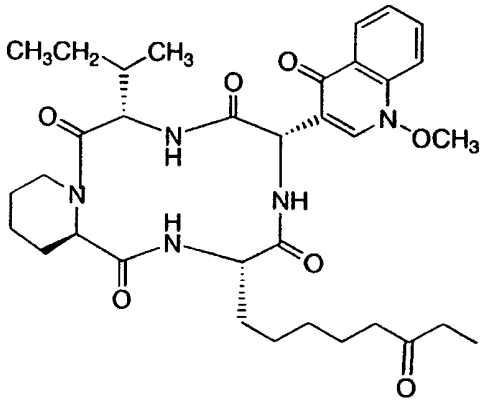
ni is 0 to 2;

mii is 0 to 7;

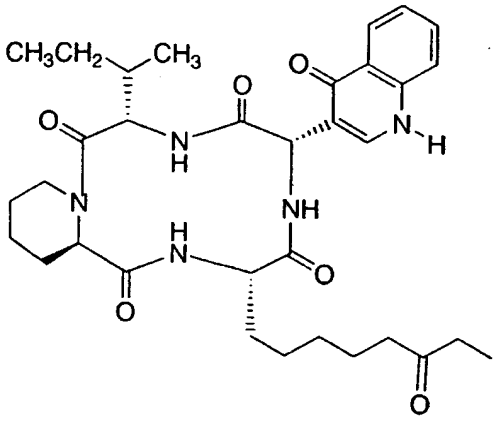
nii is 0 to 7;

v is 0 to 3; and

excluding apicidin, N-desmethoxy apicidin and compounds represented by chemical Formula IIA and chemical Formula IIB:



IIA



IIB

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is
(1) $-CH_2-$,
(2) $-C(O)-$,
(3) $-CH(OR^a)-$,
(4) $=CH-$, or
(5) not present; and

R_1 is
(1) R_7,
(2) $C(O)R_7$,
(3) CN,
(4) CO_2R^b,
(5) $C(O)N(OR^b)R^c$,
(6) $C(O)NR^cR^d$,
(7) $NHCO_2R^b$,
(8) $NHC(O)NR^cR^d$,
(9) $(C_0\text{-}C_4alkyl)OR^a$,
(10) $(C_0\text{-}C_4alkyl)OCO_2R^b$,
(11) $(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,
(12) $C(O)NR^cNR^cR^d$,
(13) $C(O)NR^cSO_2R^b$,

(21) $OS(O)_{ni}R_7$,

(22) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,

(23) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, (C_0-C_6alkyl)aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(24) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(25) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

3. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is
(1) $-CH_2-$,
(2) $-C(O)-$,
(3) $-CH(OR^a)-$,
(4) $=CH-$, or
(5) not present;

R_1 is
(1) R_7,
(2) $C(O)R_7$,
(3) CN,
(4) CO_2R^b,
(5) $C(O)N(OR^b)R^c$,
(6) $C(O)NR^cR^d$,
(7) $NHCO_2R^b$,
(8) $NHC(O)NR^cR^d$,
(9) $(C_0\text{-}C_4alkyl)OR^a$,
(10) $(C_0\text{-}C_4alkyl)OCO_2R^b$,
(11) $(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,
(12) $C(O)NR^cNR^cR^d$,
(25) $C(O)NR^cSO_2R^b$,
(26) $OS(O)_{ni}R_7$,
(27) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,
(28) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, $(C_0\text{-}C_6alkyl)aryl$, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,
(29) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by

1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(30) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent; and

R_2 is

(1) optionally substituted C_2-C_{12}alkyl,

(2) optionally substituted C_2-C_{12}alkenyl,

(3) optionally substituted C_2-C_{12}alkynyl, or

(4) $(CH_2)_{nii}$-O-$(CH_2)_{mii}$ wherein nii, mii = 0 to 7,

wherein the optional substituents on the C_2-C_{12}alkyl, C_2-C_{12}alkenyl, and C_2-C_{12}alkynyl are 1 to 8 groups and each group independently is

(a) CO_2R^a,

(b) $C(O)R^b$,

(c) $C(O)N(OR^b)R^c$,

(d) $C(O)NR^cR^d$,

(e) $C(O)NR^cNR^cR^d$,

(f) $C(O)NR^cSO_2R_7$,

(g) C_3-C_8cycloalkyl,

(h) C_2-C_5alkenyl,

(i) cyano,

(j) $=NOR^a$,
(k) $=NNR^bR^c$,
(l) $=NNR^bS(O)_{ni}R_7$,
(m) $N(OR^b)C(O)NR^bR^c$,
(n) $N(OR^b)C(O)R_7$,
(o) $NHC(O)N(OR^b)R^c$,
(p) $NR^cCO_2R^b$,
(q) $NR^cC(O)NR^cR^d$,
(r) $NR^cC(S)NR^cR^d$,
(s) $NR^cC(O)R_7$,
(t) $NR^bS(O)_{ni}R_7$,
(u) $NR^cCH_2CO_2R^a$,
(v) $NR^cC(S)R_7$,
(x) $NR^cC(O)CH_2OH$,
(y) $NR^cC(O)CH_2SH$,
(z) $NR^cCH_2CO_2R^a$,
(aa) $NR^cCH_2CH(OH)R_7$,
(bb) $NR^cP(O)(OR^a)R_7$,
(cc) NY^1Y^2, wherein Y^1 and Y^2 are independently H or C_1-C_{10}alkyl,
(dd) NO_2,
(ee) $N(OR^b)C(O)R^b$,
(ff) C_1-C_{10}alkanoylamino,
(gg) OR^a,
(hh) $OS(O)_{ni}R_7$,
(ii) oxo,
(jj) OCO_2R^b,
(kk) $OC(O)NR^cR^d$,
(ll) $P(O)(OR^a)_2$,
(mm) $P(O)(OR^a)R_7$,
(nn) $SC(O)R_7$,
(oo) $S(O)_{ni}R_7$,
(pp) SR_7,
(qq) $S(O)_{ni}NR^cR^d$,

(rr) $NR^cCH_2CO_2R^a$,
(ss) diazo,
(tt) C_1-C_5 perfluoroalkyl,
(uu) $B(O)(OR^a)OR^a$,
(xx) halogen,
(yy) aryl(C_0-C_5alkyl), wherein the aryl is optionally substituted with 1 to 3 groups, wherein each group independently is R^f, or
(xxi) a 3- to 8-membered heterocycle containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is R^f, and the heterocycle may be saturated or partly unsaturated.

4. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

5. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein:

X is
(1) $-CH_2-$,
(2) $-C(O)-$, or
(3) not present; and

R_1 is
(1) R_7,
(2) $C(O)R_7$,
(3) CN,
(4) CO_2R^b,
(5) $C(O)N(OR^b)R^c$,
(6) $C(O)NR^cR^d$,
(7) $NHCO_2R^b$,
(8) $NHC(O)NR^cR^d$,
(9) (C_0-C_4alkyl)OR^a,
(10) (C_0-C_4alkyl)OCO_2R^b,

(11) $(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,

(12) $C(O)NR^cNR^cR^d$,

(19) $C(O)NR^cSO_2R^b$,

(20) $OS(O)_{ni}R_7$,

(21) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,

(22) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, $(C_0$-$C_6alkyl)aryl$, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(23) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(24) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is

oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

6. The compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

7. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein:

X is (1) $-CH_2-$,
(2) $-C(O)-$, or
(3) not present; and

R_1 is (1) R_7,
(2) $C(O)R_7$,
(15) CO_2R^b,
(16) $C(O)N(OR^b)R^c$,
(17) $C(O)NR^cR^d$,
(18) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, (C_0-C_6alkyl)aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,
(19) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c

substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(20) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

8. The compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

9. The compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein:

X is (1) $-CH_2-$,
(2) $-C(O)-$, or
(3) not present;

R_1 is (1) R_7,
(9) $C(O)R_7$,
(10) CO_2R^b,
(11) $C(O)N(OR^b)R^c$,
(12) $C(O)NR^cR^d$,
(13) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, (C_0-C_6alkyl)aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein

the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(14) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(15) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent;and

R_2 is

(1) optionally substituted C_2-C_{12}alkyl,

(2) optionally substituted C_2-C_{12}alkenyl,

(3) optionally substituted C_2-C_{12}alkynyl, or

(4) $(CH_2)_{nii}$-O-$(CH_2)_{mii}$ wherein nii, mii = 0 to 7,

wherein the optional substituents on the C_2-C_{12}alkyl, C_2-C_{12}alkenyl, and C_2-C_{12}alkynyl are 1 to 5 groups and each group independently is

(a) CO_2R^a,

(b) $C(O)R^b$,

(c) $C(O)N(OR^b)R^c$,

(d) $C(O)NR^cR^d$,

(e) $C(O)NR^cNR^cR^d$,
(f) $C(O)NR^cSO_2R_7$,
(g) C_3-C_8cycloalkyl,
(h) C_2-C_5alkenyl,
(i) cyano,
(j) $=NOR^a$,
(k) $=NNR^bR^c$,
(l) $=NNR^bS(O)_{ni}R_7$,
(m) $N(OR^b)C(O)NR^bR^c$,
(n) $N(OR^b)C(O)R_7$,
(o) $NHC(O)N(OR^b)R^c$,
(p) $NR^cCO_2R^b$,
(q) $NR^cC(O)NR^cR^d$,
(r) $NR^cC(S)NR^cR^d$,
(s) $NR^cC(O)R_7$,
(t) $NR^bS(O)_{ni}R_7$,
(u) $NR^cCH_2CO_2R^a$,
(v) $NR^cC(S)R_7$,
(x) $NR^cC(O)CH_2OH$,
(y) $NR^cC(O)CH_2SH$,
(z) $NR^cCH_2CO_2R^a$,
(aa) $NR^cCH_2CH(OH)R_7$,
(bb) $NR^cP(O)(OR^a)R_7$,
(cc) NY^1Y^2, wherein Y^1 and Y^2 are independently H or methyl,
(dd) NO_2,
(ee) $N(OR^b)C(O)R^b$,
(ff) C_1-C_3alkanoylamino,
(gg) OR^a,
(hh) $OS(O)_{ni}R_7$,
(ii) oxo,
(jj) OCO_2R^b,
(kk) $OC(O)NR^cR^d$,
(ll) $P(O)(OR^a)_2$,

(mm) $P(O)(OR^a)R_7$,
(nn) $SC(O)R_7$,
(oo) $S(O)_{ni}R_7$,
(pp) SR_7,
(qq) $S(O)_{ni}NR^cR^d$,
(rr) $NR^cCH_2CO_2R^a$,
(ss) diazo,
(tt) C_1-C_5 perfluoroalkyl,
(uu) $B(O)(OR^a)OR^a$,
(zz) halogen,
(aaa) aryl(C_0-C_5alkyl), wherein the aryl is optionally substituted with 1 to 3 groups, wherein each group independently is R^f, or
(xxii) a 3- to 6-membered heterocycle containing from 1 to 4 heteroatoms, each heteroatom independently is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is R^f, and the heterocycle may be saturated or partly unsaturated.

10. The compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

11. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:
R3 each independently is
(1) hydrogen, or
(2) halogen,
(3) OR^a,
(4) C_1-C_4alkyl, or
(5) C_1-C_4aryl; and
R^a is
(1) hydrogen,
(2) optionally substituted C_1-C_6alkyl,

(8) optionally substituted C_3-C_6alkenyl,
(9) optionally substituted C_2-C_4alkanoyl,
(5) optionally substituted C_3-C_4alkenoyl,
(6) optionally substituted aroyl,
(7) optionally substituted aryl,
(8) optionally substituted C_5-C_6cycloalkanoyl,
(9) optionally substituted C_1-C_4alkylsulfonyl,
(10) optionally substituted C_5-C_6cycloalkyl,
(15) optionally substituted C_5-C_6cycloalkenyl,

wherein the optional substituents on the C_1-C_6alkyl, C_3-C_6alkenyl, C_2-C_4alkanoyl, C_3-C_4alkenoyl, aroyl, aryl, C_5-C_6cycloalkanoyl, C_1-C_4alkylsulfonyl, C_5-C_6cycloalkyl and C_5-C_6cycloalkenyl are from 1 to 10 groups, wherein each group independently is hydroxy, methoxy, aryl methoxy, NR^xR^x, CO_2R^b, $CONR^cR^d$, or halogen,

(16) CF_3,
(17) arylsulfonyl optionally substituted with 1 to 3 groups, wherein each group independently is methyl, CF_3, nitro, halogen or cyano, or
(18) a 5- or 6-membered heterocycle containing 1 to 3 heteroatoms, wherein each heteroatom is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is methyl, CF_3, NMe_2, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, and wherein the heterocycle may be saturated or partly unsaturated.

12. The compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein:
R3 each independently is

(1) hydrogen,
(2) halogen,
(3) OR^a,
(4) C_1-C_4alkyl, or
(5) C_1-C_4aryl;);

R^a is (1) hydrogen,
(2) optionally substituted C_1-C_6alkyl,
(10) optionally substituted C_3-C_6alkenyl,
(11) optionally substituted C_2-C_4alkanoyl,
(5) optionally substituted C_3-C_4alkenoyl,
(6) optionally substituted aroyl,
(7) optionally substituted aryl,
(8) optionally substituted C_5-C_6cycloalkanoyl,
(9) optionally substituted C_1-C_4alkylsulfonyl,
(10) optionally substituted C_5-C_6cycloalkyl,
(15) optionally substituted C_5-C_6cycloalkenyl,
wherein the optional substituents on the C_1-C_6alkyl, C_3-C_6alkenyl, C_2-C_4alkanoyl, C_3-C_4alkenoyl, aroyl, aryl, C_5-C_6cycloalkanoyl, C_1-C_4alkylsulfonyl, C_5-C_6cycloalkyl and C_5-C_6cycloalkenyl are from 1 to 10 groups, wherein each group independently is hydroxy, methoxy, aryl methoxy, NR^xR^x, CO_2R^b, $CONR^cR^d$, or halogen,
(16) CF_3,
(17) arylsulfonyl optionally substituted with 1 to 3 groups, wherein each group independently is methyl, CF_3, nitro, halogen or cyano, or
(18) a 5- or 6-membered heterocycle containing 1 to 3 heteroatoms, wherein each heteroatom is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is methyl, CF_3, NMe_2, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, and wherein the heterocycle may be saturated or partly unsaturated.

X is (1) $-CH_2-$,
(2) $-C(O)-$,
(5) $=CH-$, or
(6) not present; and

R_1 is (1) R_7,
(2) $C(O)R_7$,
(3) CN,

(4) CO_2R^b,

(5) $C(O)N(OR^b)R^c$,

(6) $C(O)NR^cR^d$,

(7) $NHCO_2R^b$,

(8) $NHC(O)NR^cR^d$,

(9) $(C_0\text{-}C_4alkyl)OR^a$,

(10) $(C_0\text{-}C_4alkyl)OCO_2R^b$,

(11) $(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,

(12) $C(O)NR^cNR^cR^d$,

(19) $C(O)NR^cSO_2R^b$,

(20) $OS(O)_{ni}R_7$,

(21) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,

(22) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, $(C_0\text{-}C_6alkyl)$aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(23) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(24) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered

heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

13. The compound according to 12, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

14. The compound according to claim 11, or a pharmaceutically acceptable salt thereof, wherein:

R3 each independently is

(1) hydrogen,
(2) halogen,
(3) OR^a,
(4) C_1-C_4alkyl, or
(5) C_1-C_4aryl;);

R^a is
(1) hydrogen,
(5) optionally substituted C_1-C_6alkyl,
(6) optionally substituted C_3-C_6alkenyl,
(7) optionally substituted C_2-C_4alkanoyl,
(5) optionally substituted C_3-C_4alkenoyl,
(6) optionally substituted aroyl,
(7) optionally substituted aryl,
(8) optionally substituted C_5-C_6cycloalkanoyl,
(9) optionally substituted C_1-C_4alkylsulfonyl,
(10) optionally substituted C_5-C_6cycloalkyl,
(15) optionally substituted C_5-C_6cycloalkenyl,

wherein the optional substituents on the C_1-C_6alkyl, C_3-C_6alkenyl, C_2-C_4alkanoyl, C_3-C_4alkenoyl, aroyl, aryl, C_5-C_6cycloalkanoyl, C_1-C_4alkylsulfonyl, C_5-C_6cycloalkyl and C_5-C_6cycloalkenyl are from 1

to 10 groups, wherein each group independently is hydroxy, methoxy, aryl methoxy, NR^xR^x, CO_2R^b, $CONR^cR^d$, or halogen,

(16) CF_3,

(17) arylsulfonyl optionally substituted with 1 to 3 groups, wherein each group independently is methyl, CF_3, nitro, halogen or cyano, or

(18) a 5- or 6-membered heterocycle containing 1 to 3 heteroatoms, wherein each heteroatom is oxygen, sulfur or nitrogen, wherein the heterocycle is optionally substituted by 1 to 3 groups, wherein each group independently is methyl, CF_3, NMe_2, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, and wherein the heterocycle may be saturated or partly unsaturated;

X is (1) $-CH_2-$,

(5) $-C(O)-$,

(6) $=CH-$, or

(7) not present; and

R_1 is (1) R_7,

(2) $C(O)R_7$,

(21) CO_2R^b,

(22) $C(O)N(OR^b)R^c$,

(23) $C(O)NR^cR^d$,

(24) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, (C_0-C_6alkyl)aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(25) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by

1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, C(O)NR^cR^d, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(26) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, C(O)NR^cR^d, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

15. The compound according to claim 14, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

16. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

R_6 each independently is

(1) O,
(2) S, or
(3) H;

X is
(1) $-CH_2-$,
(2) $-C(O)-$,
(5) $=CH-$, or
(6) not present; and

R_1 is
(1) R_7,

(2) $C(O)R_7$,

(3) CN,

(4) CO_2R^b,

(5) $C(O)N(OR^b)R^c$,

(6) $C(O)NR^cR^d$,

(7) $NHCO_2R^b$,

(8) $NHC(O)NR^cR^d$,

(9) $(C_0\text{-}C_4alkyl)OR^a$,

(10) $(C_0\text{-}C_4alkyl)OCO_2R^b$,

(11) $(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,

(12) $C(O)NR^cNR^cR^d$,

(13) $C(O)NR^cSO_2R^b$,

(19) $OS(O)_{ni}R_7$,

(20) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,

(21) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, $(C_0\text{-}C_6alkyl)aryl$, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(22) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(23) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

17. The compound according to claim 16, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

18. The compound according to claim 16, or a pharmaceutically acceptable salt thereof wherein:

R3 each independently is

(1) hydrogen,
(2) halogen,
(3) OR^a,
(4) C_1-C_4alkyl, or
(5) C_1-C_4aryl;

R_6 each independently is

(1) O,
(2) S, or
(3) H;

X is
(1) $-CH_2-$,
(2) $-C(O)-$,
(3) $=CH-$, or
(5) not present; and

R_1 is
(1) R_7,
(2) $C(O)R_7$,
(3) CN,

(4) CO_2R^b,

(5) $C(O)N(OR^b)R^c$,

(6) $C(O)NR^cR^d$,

(7) $NHCO_2R^b$,

(8) $NHC(O)NR^cR^d$,

(9) $(C_0\text{-}C_4alkyl)OR^a$,

(10) $(C_0\text{-}C_4alkyl)OCO_2R^b$,

(11) $(C_0\text{-}C_4alkyl)OC(O)NR^cR^d$,

(12) $C(O)NR^cNR^cR^d$,

(19) $C(O)NR^cSO_2R^b$,

(20) $OS(O)_{ni}R_7$,

(21) $NR^bS(O)_{ni}R_7$, wherein ni is from 0 to 2,

(22) a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, $(C_0\text{-}C_6alkyl)aryl$, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent,

(23) a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide, or

(24) a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered

heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, $C(O)NR^cR^d$, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an R^c substituent.

19. The compound according to claim 18, or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2.

20. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X is preferably $-CH_2-$.

21. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X is preferably $-C(O)-$.

22. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X is preferably not present.

23. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is preferably a 3- to 8-membered heterocycle containing 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, NR^cR^d, oxo, thiono, OR^a, $S(O)_{ni}R^a$ (where ni = 0, 1 or 2), $C(O)R^a$, $C(O)NR^cR^d$, cyano, (C_0-C_6alkyl)aryl, CO_2R^b, or halogen, and each group may be saturated, partly unsaturated or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an R^c substituent.

24. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is preferably a benzene ring fused to a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, optionally substituted by 1 to 4 groups each independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl,

amino, oxo, thiono, C(O)NRcRd, cyano, CO_2R^b or halogen, each group may be saturated, partly unsaturated, or fully unsaturated, wherein the heteroatoms are each independently oxygen, sulfur, or nitrogen, in which the nitrogen optionally has an Rc substituent, and wherein the benzene/heterocycle fused ring is attached at any site to X or to the tetrapeptide

25. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is preferably a 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms fused to a second 4- to 8-membered heterocyclic ring with from 1 to 4 heteroatoms, each heterocyclic ring independently optionally substituted by 1 to 4 groups, each group independently is C_1-C_5alkyl, C_2-C_5alkenyl, C_1-C_5perfluoroalkyl, amino, oxo, thiono, C(O)NRcRd, cyano, CO_2R^b or halogen, wherein each heterocycle may be saturated, partly unsaturated or fully unsaturated, and wherein each heteroatom independently is oxygen, sulfur, or nitrogen, and the nitrogen optionally has an Rc substituent.

26. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

27. A method for the treatment of protozoal infections comprising the step of administering, to a host in need of such treatment, a non-toxic amount of a composition according to claim 1 effective to inhibit a histone deacetylase activity of the infecting protozoa.

28. A method for the prevention of protozoal infections comprising the step of administering to a host a non-toxic effective preventative amount of a composition according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/19627

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/395, 38/12; C07D 257/10; C07K 5/12

US CL :514/11,183; 530/321; 540/460

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/9, 11, 183; 530/317, 321; 540/460

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, CHEMICAL ABSTRACTS, DIALOG

search terms: apicidin, tetrapeptide, antiprotozoa, histone deacetylase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,620,953 A (CANNOVA ET AL) 15 April 1997 (15/04/97), see entire document, especially the Abstract, column 1, line 49 - column 2, line 6, claims 1-4.	1-28
X	US 5,922,837 A (MEINKE ET AL) 13 July 1999 (13/07/99), see entire document, especially the Abstract, column 6, lines 32-46, column 7, lines 20-34.	1-28
X,P	EP 1 010 705 A1 (JAPAN ENERGY CORPORATION) 21 June 2000 (21/06/2000), see entire document, especially pages 43, 44, 46-48, claims 1-8.	1-26, 28

[X] Further documents are listed in the continuation of Box C. [] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

11 SEPTEMBER 2000

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/19627

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DARKIN-RATTRAY et al. Apicidin: A novel antiprotozoal agent that inhibits parasite histone deacetylase. Proceedings Of The National Academy Of Sciences USA. November 1996, Volume 93, pages 13143-13147, especially Figure 1B, compound cly-2, and page 13145, column 2, third full paragraph.	1-26, 28
A	SINGH et al. Apicidins: Novel Cyclic Tetrapeptides as Coccidiostats and Antimalarial Agents from Fusarium pallidoroseum. Tetrahedron Letters. 1996, Volume 37, Number 45, pages 8077-8080.	1-28

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